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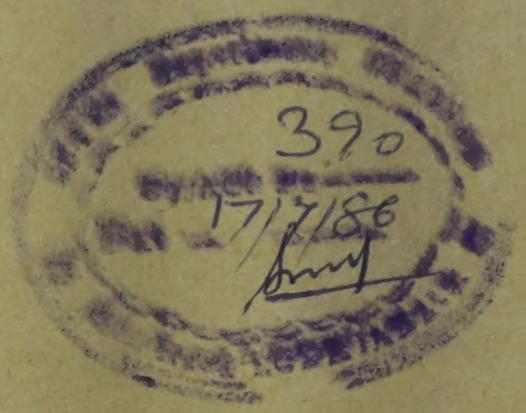

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Indian Journal of Chemistry

Sect. B: Organic Chemistry, Including Medicinal Chemistry

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Rearrangement/Oxygen Functionalization of Longifolene into Culmorin, a Longibornane Diol Mould Metabolite of *Fusarium culmorum*†

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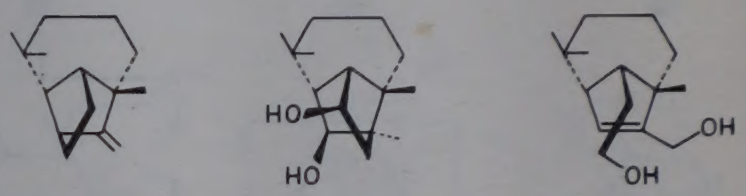
Received 2 *December* 1985; *accepted* 7 *January* 1986

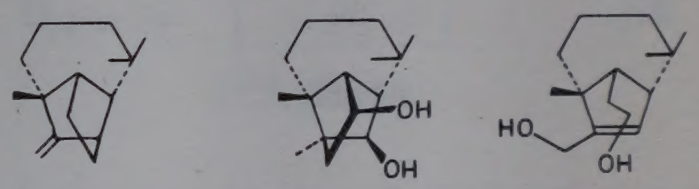
A ten-step synthesis of (+)-culmorin (**2a**) from longifolene (**1a**) which involves formation of 10-ketolongifolene (**18**) as the key intermediate is described. The known 11-hydroxylongicyclene (**15**), when exposed to hydrogen bromide in acetic acid gives the novel 8, 11-dibromolongibornane (**16**). On reaction with silver perchlorate in aqueous acetone followed by Jones' oxidation, **16** gives the viable 10-ketolongifolene (**18**) in 25% yield. When subjected to acid-catalyzed Wagner-Meerwein rearrangement/hydration reaction with 50% aq. sulphuric acid-acetic acid, **18** affords a mixture of keto olefins (**21**) and three keto acetates (**22**), (**23**) and (**24**). The required 8-β-acetoxy-11-ketolongibornane (**22**), on hydrolysis/oxidation affords (+)-culmorin diketone (**10**). Since this diketone has been earlier reduced to the diol **2a**, the elaboration of **1a** to **10** constitutes a synthesis of (+)-**2a** itself.

Two microbial secondary metabolites (−)-culmorin[1] (**2b**)/(+)-secolongifolene diol[2] (**3b**), of close biogenetic relationship with (−)-longifolene[2a] (**1b**), are known in the literature for a long time. While both are diols and have configurations inverse of that found in the plant-derived (+)-longifolene (**1a**), **2b** is tricyclic but **3b** is bicyclic as a result of microbial fragmentation. As part of our efforts aimed at conversion of (+)-**1a** into other naturally occurring sesquiterpenoids, we have recently described[3] the transformation of (+)-**1a** into (−)-**3a**. This paper deals with studies directed towards elaboration of (+)-culmorin (**2a**) from the **1a**.

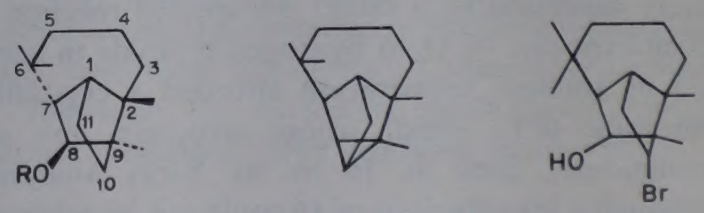
The transformation of **1a** into (+)-**2a** formally a 11-β-hydroxy derivative of longiborneol (**4**) constitutes essentially an unsolved problem of functionalization of the inaccessible C-11 site of the longibornane skeleton. In this connection an abortive attempt aimed at a difunctional longibornane (**6**) by hypobromous acid-mediated cyclopropane ring-opening/rearrangement/functionalization of longicyclene (**5**) was reported[4] by us recently. Similar cleavage/1, 2-shift/hydroxylation sequence attempted on 11-ketolongicyclene (**7**) to generate **8** by acid-catalyzed 'hydration' reagents (aqueous sulphuric acid-acetic acid, trifluoroacetic acid in dichloromethane) also met with failure and only unchanged material was recovered. Later, inspite of the successful generation[5] of 8-bromo-11-keto longibornane (**9**) from 11-ketolongicyclene (**7**) by the action of hydrogen bromide in acetic acid, the next solvolysis step met with failure because of an undesired transannular reaction; the product obtained after Jones' oxidation was not



(+)-1a (+)-2a (−)-3a



(−)-1b (−)-2b (+)-3b



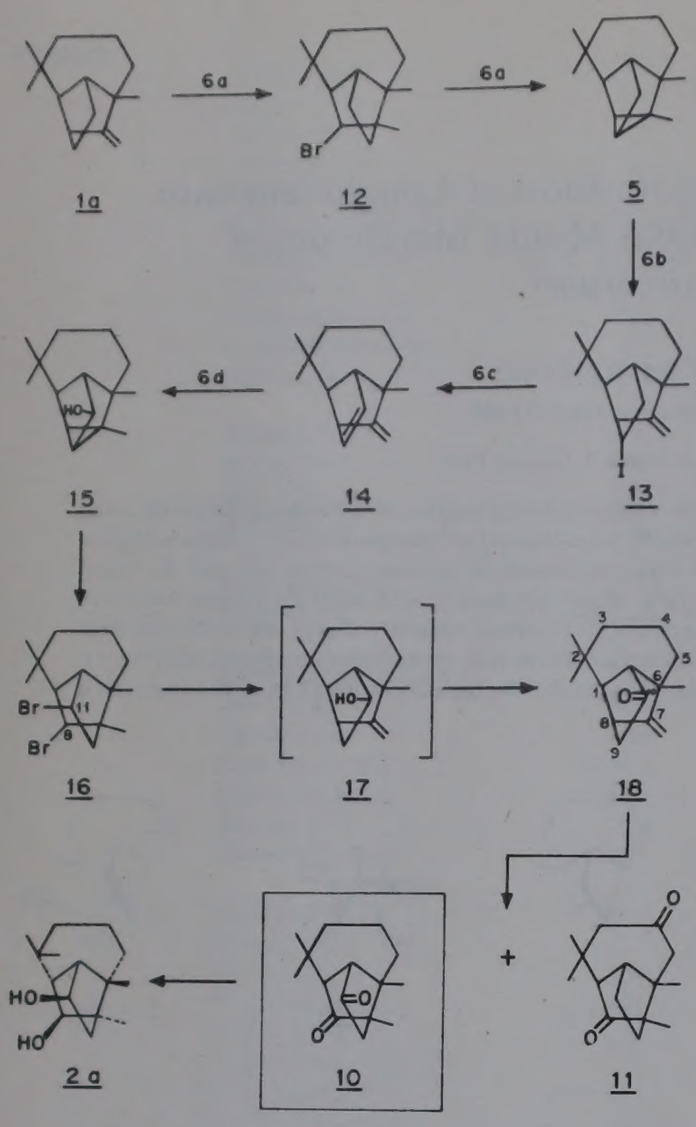
4: R=H
4a: R=Ac

5 6

the expected culmorin diketone (**10**) but its transannular isomer[5] **11**. We now describe the first successful generation of **10** from longifolene (**1a**) in nine steps; since this diketone has been earlier reduced to culmorin (**2**), the elaboration of **1** into **10** constitutes a synthesis of **2**.

The strategy which finally gave the targetted **10** is depicted in Scheme 1. The first five steps (Scheme 1)

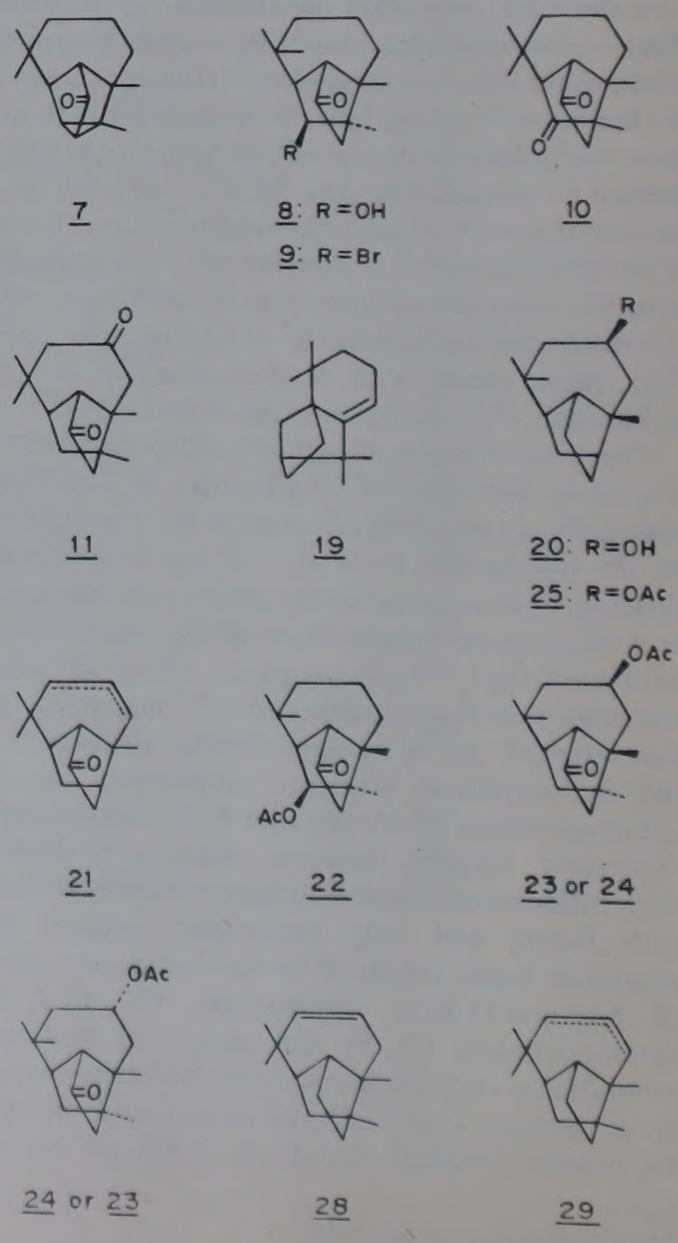
†NCL Communication No. 3950.



SCHEME 1

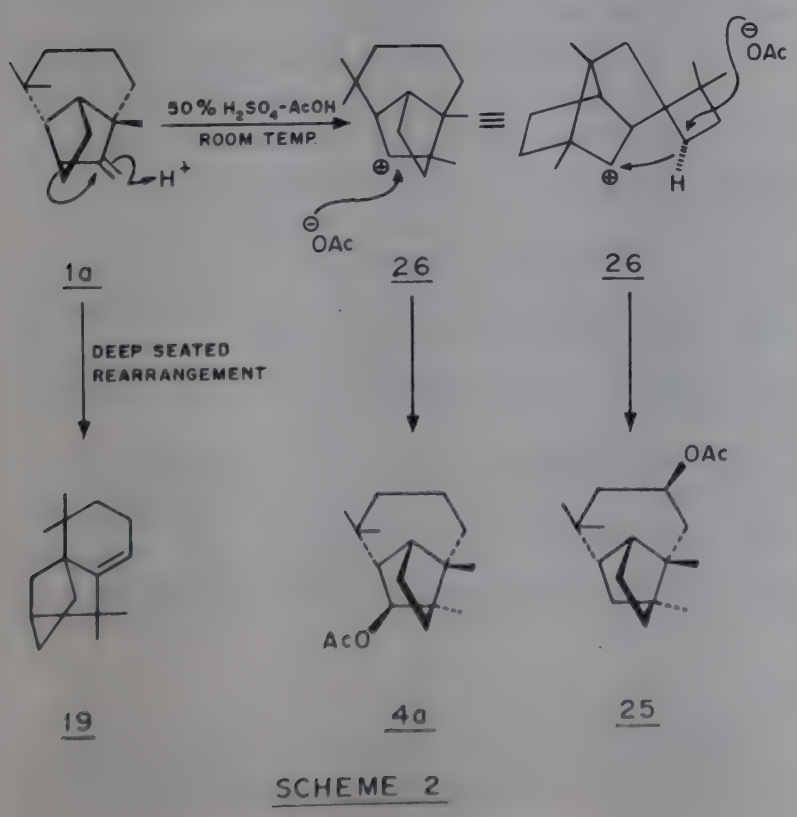
which elaborate longifolene **1a** into the crucial 11-hydroxylongicyclene (**15**) have been described earlier[6]. A viable 8,11-difunctionalized longibornane was finally generated by a rather unexpected reaction in which exposure of **15** to hydrogen bromide in acetic acid at ambient temperature afforded a crystalline dibromide (80% yield) whose structure was unambiguously fixed as **16** by its X-ray analysis[7]. Although a bis-solvolysis of **16** could not be achieved, silver perchlorate in aqueous acetone (room temperature/18 hr) gave a mixture‡ of secondary alcohols which could only be separated by chromatography over silica gel in the form of their ketones (Jones' oxidation) to furnish a key intermediate, 10-ketolongifolene (**18**), in 25% yield. In conformity with the assigned structure, **18** exhibited an IR band at 1750 cm^{-1} (five-membered ring ketone) and two vinylic PMR 1H-singlets at δ 4.78, 5.05 diagnostic of an exo-methylene; on Wolff-Kishner reduction, **18** gave longifolene (**1a**) as the deoxo compound.

Acid-catalyzed Wagner-Meerwein rearrangement/hydration of the olefinic bond in **18** followed by Jones' oxidation of the resulting ketoalcohol (**8**) appeared to be the only way of converting it into culmorin diketone (**10**). However, when **18** was exposed to Bertram-Walbaum reagent (50% aq. sulphuric acid-acetic acid) at room temperature, no reaction took place. It may be recalled[8] that under these conditions longifolene (**1a**) generates longiborneol (**4**) in less than 10% yield; the other two products being isolongifolene (**19**) (60%) and the transannular alcohol[8b] (**20**) (20%). The sluggishness of the double bond in **18** towards the hydration reaction was obviously due to the presence of a keto group at C-10 and hence more energetic conditions had to be optimized. Thus, **18** was heated with Bertram-Walbaum reagent on a steam-bath for 3 days

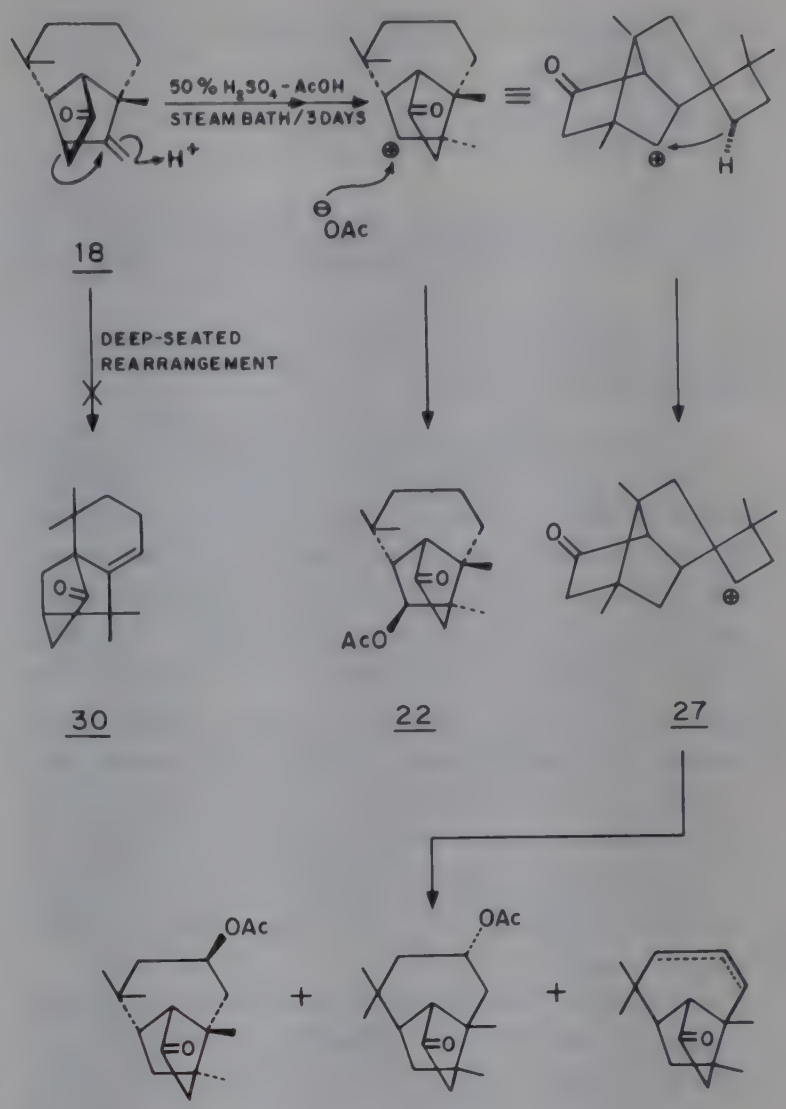


‡The other rearrangement products formed in the interesting silver ion-assisted solvolysis of 8, 11-dibromolongibornane (**16**) will be described elsewhere.

and the resulting complex mixture carefully chromatographed on a column of silica gel when the required 8-β-acetoxy-11-ketolongibornane (**22**) could be separated pure in 12% yield from the less polar keto olefins (**21**) ($AgNO_3$-TLC; IR/PMR; 30%) and two other slightly more polar ketoacetates (**23**/**24**) (21%). The characteristic PMR splitting pattern of the secondary acetate proton in the case of 8-β-acetoxylongibornane[8b] (**4a**) (*dd*, δ 5.20, $J_1 = 6$ Hz, $J_2 = 2$ Hz) was present only in **22**. The other two acetates, also secondary, proved to be epimeric (both showing a broad multiplet between δ 4.47 to 5.30, characteristic of $-CH_2-CHOAc-CH_2-$) at the transannular C-4 position; on hydrolysis followed by oxidation both gave isoculmorin[5] (**11**). Mechanistically, formation of an epimeric pair of transannular acetates (**23**/**24**) during reaction of **18** with 50% aq. sulphuric acid-acetic acid, is in sharp contrast to the generation of a single epimer, 4-β-acetoxylongibornane[8b] (**25**) from **1a**. In the latter case, **25** evidently arises from the carbonium ion (**26**) (Scheme 2) via a transannular attack by the acetate nucleophile on C-4 with concomitant migration of the α-hydrogen at C-4 to the electron-deficient centre. The formation of an epimeric pair of acetates (**23**/**24**) in the case of keto olefin (**18**) indicates that a C-4 carbocation (**27**, Scheme 3) is distinctly formed here, the reaction conditions for **18** being considerably more drastic (steam bath/3 days) as compared to those for **1a** (room temperature). Further more, the C-4 carbocation (**27**) also suffered an elimination to generate the keto olefins (**21**) (30%); on Wolff-Kishner reduction of **21** followed by $AgNO_3$-silica gel chromatography, atleast one olefin was obtained pure and characterised as longiborn-4-ene[9]



SCHEME 2



SCHEME 3

(**28**). In the case of **1a**, the corresponding elimination product **29** was not formed at all, the major olefin (60%) generated being isolongifolene (**19**); such a deep-seated rearrangement (Scheme 3, **30**), however, was not observed during hydration of ketolongifolene (**18**). Finally, hydrolysis of 8-acetoxy-11-ketolongibornane (**22**) followed by oxidation gave (+)-culmorin diketone[1b] (**10**) (m.p. 104°; identified by IR/PMR).

Experimental Procedure

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na_2SO_4. Silver perchlorate[10] was freshly prepared and dried. IR spectra (ν_{max} in cm^{-1}) were recorded as smears (liquids) or nujol mulls (solids) on a Pye-Unicam SP-3 IR spectrophotometer. PMR spectra were taken on Varian T60/FT-80A Bruker WH-90 spectrometers and mass spectra (MS) on a CEC spectrometer model 21-110B, using an ionizing voltage of 70 eV and a direct inlet system. Optical rotations were measured on a JASCO:DIP-181 digital polarimeter. The X-ray data for compound **16**

were collected on a Enraf-Nonius CAD4-11M diffractometer.

11-Hydroxylongicyclene (**15**)/*11-ketolongicyclene* (**7**)

These were prepared by hydration/hydrolysis and oxidation of dehydrolongifolene (**14**) as reported[5,6a].

Action of HBr-AcOH on **15**: *Formation of* 8,11-*dibromolongibornane* (**16**)

A mixture of **15** (6 g) and 32% HBr-AcOH (40 ml) was kept at room temperature (18 hr). The separated crystalline dibromide **16** was filtered and recrystallised from ethanol. The mother liquor was diluted with water (50 ml), extracted with ether, washed with 5% aq. $NaHCO_3$, brine, dried and solvent removed. The crude product was chromatographed on silica gel/IIa (30 g). Elution with light petroleum gave some more crystalline dibromide **16**; m.p. 124° (EtOH) (total yield 7.5 g, 80%); IR: 925, 780, 740; PMR (CCl_4): δ 0.87, 0.97, 1.03, 1.12 (four tertiary methyl singlets), 4.08 (*dd*, 1H, $C_8-CH-Br$, $J_1=7$ Hz, $J_2=2$ Hz), 4.45 (*m*, 1H, $C_{11}-CH-Br$). (Found: C, 49.7; H, 6.6; Br, 44.1. $C_{15}H_{24}Br_2$ requires C, 49.7; H, 6.6; Br, 43.6%).

X-ray[7] data of **16** were collected using the $\omega/2\theta$ scan technique upto $2\theta=48°$. Three standard reflections were monitored after every 2000 seconds of exposure time to check for crystal decay, if any. The structure was refined using full matrix least square technique with anisotropic temperature factors for non-hydrogen atoms. Hydrogen atoms were fixed based on stereochemical consideration and their positions verified by difference Fourier synthesis.

Solvolysis of 8,11-*dibromo longibornane* (**16**): *Formation of* 10-*ketolongifolene* (**18**)

To a solution of **16** (8 g) in 50% aq. acetone (150 ml) silver perchlorate (9.8 g) was added and stirred at room temperature (18 hr). The reaction mixture was filtered, filtrate diluted with water (200 ml), extracted with EtOAc (3 × 100 ml), washed with brine, dried and solvent removed. The crude product (5 g) was chromatographed on silica gel/IIa (180 g, 80 cm × 10 cm). Fr. 1, light petroleum, 4 × 100 ml, mixture. Fr. 2, benzene, 6 × 100 ml, pure new alcohol[8] (3.5 g). Fr. 3, 1% EtOAc in benzene, 8 × 100 ml, mixture.

Fr. 3, (1.5 g), was oxidised (Jones' reagent) and the resulting mixture of keto olefins (1.4 g) chromatographed on silica gel/IIa (80 g, 60 cm × 6.5 cm). Fr. 1, light petroleum-benzene (1:1), 4 × 100 ml, pure (0.1 g), its structure will be discussed elsewhere). Fr. 2, light petroleum-benzene (1:1), 5 × 100 ml, 10-ketolongifolene (**18**), b.p. 140/0.5 mm (1.25 g, 26%); IR (smear): 3090, 1750, 1660, 1420, 1160, 890; PMR (CCl_4): δ 0.97 (*s*, 9H, three tertiary methyl), 4.78 and 5.05 (two *s*, 1H each, $>C=CH_2$): MS: *m/z* 218 (M^+, base peak) (Found: C, 83.7; H, 10.4. $C_{15}H_{22}O$ requires C, 82.6; H, 10.1%).

Wolff-Kishner reduction of 10-*ketolongifolene* (**18**): *Formation of longifolene* (**1a**)

A mixture of **18** (0.3 g), hydrazine hydrate (85%, 6 ml), KOH (1.5 g) and diethylene glycol (75 ml) was refluxed for 1 hr. Water and excess hydrazine were then distilled out and refluxing continued for 3 hr. The cooled reaction mixture was diluted with water (50 ml), extracted with light petroleum, washed with water, brine, dried, solvent removed and the crude product chromatographed on silica gel/IIa (20 g, 20 cm × 1 cm). Elution with light petroleum gave longifolene (**1a**) (0.65 g, 55%) identified by IR/PMR.

Hydration of 10-*ketolongifolene* (**18**): *keto olefins* (**21**), *Formation of ketoacetates* (**22**) *and* (**23** *or* **24**)

A mixture of **18** (1.5 g), gl. AcOH (20 ml) and 50% aq. H_2SO_4 (5 ml) was heated on a steam-bath for 3 days. The reaction mixture was diluted with water (50 ml), extracted with benzene, washed with water, brine, dried, solvent removed and the crude product chromatographed on silica gel/IIa (100 g, 20 × 6.5 cm) (with TLC monitoring). Fr. 1, benzene, 6 × 50 ml, pure. Fr. 2, 1% EtOAc in benzene, 2 × 50 ml, pure. Fr. 3, 1% EtOAc in benzene, 3 × 50 ml, pure. Fr. 4, 2% EtOAc in benzene, 4 × 50 ml mixture. Fr. 5, 2% EtOAc in benzene, 5 × 50 ml, pure.

Fr. 1, was distilled to give keto olefins **21** as a colourless liquid, b.p. 130°/0.5 mm (0.53 g, 30%). $AgNO_3$ silica gel TLC: 2 spots.

Fr. 2, was distilled to furnish **22** as a liquid b.p. 160°/0.5 mm (bath) (0.2 g, 12%); IR (smear): 1760, 1740, 1230, 1140; PMR ($CDCl_3$): δ 0.88, 0.96, 1.00, 1.06 (four tertiary methyl singlets), 2.08 (*s*, 3H, $COCH_3$), 5.50 (*dd*, 1H, C-8-C*H*-OAc, $J_1=6$ Hz, $J_2=2$ Hz).

Fr. 3, was distilled to give **23** or **24** as colourless liquid), b.p. (bath) 160°/0.5 mm (0.1 g, 6%); IR (smear): 1750, 1740, 1260; PMR ($CDCl_3$): 0.88, 0.90, 1.02, 1.08 (four tertiary methyl singlets), 2.02 (*s*, 3H, $COCH_3$) and 5.22 (*bm*, 1H, C-4-C*H*-OAc).

Fr. 5, was distilled to obtain **24** or **23** as liquid, b.p. (bath) 160°/0.5 mm (0.25 g, 15%); IR (smear): 1760, 1740, 1265; PMR ($CDCl_3$): δ 0.84, 0.97, 1.04, 1.08 (four tertiary methyl singlets), 1.97 (*s*, 3H, $COCH_3$) and 4.64 (*bm*, 1H, C-4-C*H*-OAc).

8*β*-*Acetoxylongibornane* (**4a**)

Longiborneol (**4**) was acetylated with AC_2O and pyridine at room temperature. Distillation gave **4a**; IR

[8]Structure of new alcohol will be discussed elsewhere

(smear): 1745, 1250, 930; PMR ($CDCl_3$): δ 0.72, 0.74, 0.78, 0.88 (four tertiary methyl singlets), 2.0 (*s*, 3H, $COCH_3$) and 5.2 (*dd*, 1H, C-8 $-CH-OAc$, $J_1=6$ Hz, $J_2=2$ Hz).

Hydrolysis/Jones' oxidation of keto acetate (**22**): *Formation of culmorin diketone* (**10**)[12]

Compound (**22**, 0.2 g) was hydrolysed with 10% aq. ethanolic KOH (25 ml) at room temperature (18 hr) and the crude product oxidised with Jones' reagent to give **10**[1b] as a solid m.p. 103°, $[\alpha]_D+22.8°$ ($CHCl_3$). Mould metabolite culmorin (from *Fusarium culmorum*) gave diketone with opposite rotation, $[\alpha]_D-29°$ ($CHCl_3$).

Hydrolysis/Jones' oxidation of keto acetates (**23**) *and* (**24**): *Formation of isoculmorin diketone*[5] (**11**)

The keto acetates (**23**/**24**) were hydrolysed with 10% aq. ethanolic KOH at room temperature (18 hr) and the crude product oxidised with Jones' reagent. In both the cases **11**, m.p. 111° (IR/PMR) was formed.

Wolff-Krishner reduction of the keto olefins (**21**): *Formation of longiborn-4-ene* (**27**)

A mixture of **21** (0.32 g), hydrazine hydrate (85%, 6 ml), KOH (1.5 g) and diethylene glycol (50 ml) was subjected to reduction as described earlier for **18**. The crude mixture was chromatographed on $AgNO_3$-silica gel[11] (with TLC monitoring); Fr. 1, light petroleum, 5 × 20 ml, pure longiborn-4-ene (**27**) (0.1 g, 37%), identified by IR/PMR. The following two fractions were mixtures.

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Synthesis of Murrayafoline-B & Murrayaquinone-B†

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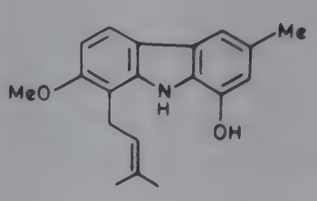
Received 23 *September* 1985; *accepted* 13 *November* 1985

Murrayafoline-B (**1**) has been synthesised starting from 7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**4**) by a sequence of reactions, such as, aromatisation, demethylation, monoacetylation, prenylation followed by methylation and finally deacetylation. Pyridinium chlorochromate oxidation of murrayafoline-B affords murrayaquinone-F (**2**) in a moderate yield.

Two novel carbazole alkaloids murrayafoline-B (**1**) and murrayaquinone-B (**2**) have recently been isolated from *Murraya euchrestifolia*[1,2] Hayata (Rutaceae) and their structures established by physicochemical methods as 1-hydroxy-7-methoxy-3-methyl-8-(3,3-dimethylallyl)-carbazole (**1**) and 7-methoxy-3-methyl-1,4-dioxo-8-(3,3-dimethylallyl)carbazole (**2**). In this paper we report the synthesis of both these alkaloids which rigorously confirms the earlier assigned structures.



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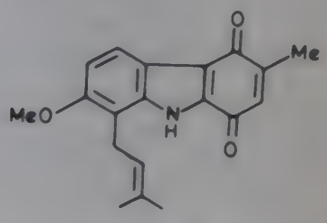

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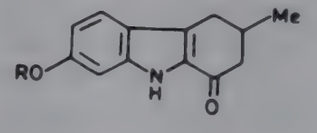
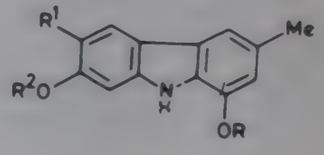
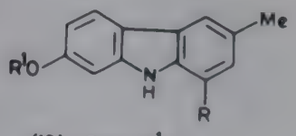


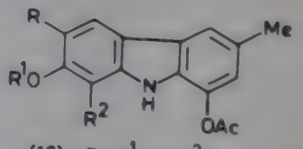
(3) R=H
(4) R=Me
(5) R=Ac



(6) $R=R^1=R^2=H$
(7) $R=R^1=H, R^2=Me$
(8) $R=Me, R^1=R^2=H$
(9) $R=R^2=H, R^1=Ac$
(10) $R=Bzl, R^1=R^2=H$
(11) $R=R^1=H, R^2=Bzl$



(12) $R=H, R^1=Ac$
(13) $R=OH, R^1=Ac$
(14) $R=OAc, R^1=H$
(15) $R=OAc, R^1=Ac$



(16) $R=R^1=H, R^2=3,3\text{-DMA}^*$
(17) $R=R^2=H, R^1=3,3\text{-DMA}$
(18) $R=3,3\text{-DMA}, R^1=R^2=H$
(19) $R=H, R^1=R^2=3,3\text{-DMA}$
(20) $R=R^1=3,3\text{-DMA}, R^2=H$
(21) $R=R^2=3,3\text{-DMA}, R^1=H$
(22) $R=H, R^1=Me, R^2=3,3\text{-DMA}$

*DMA = DIMETHYLALLYL

Aromatisation of 7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole[3] (**4**) with 10% Pd-C in diphenyl ether resulted in the formation of 1-hydroxy-7-methoxy-3-methylcarbazole (**7**), which on demethylation with HBr (48%) in gl. acetic acid afforded **6** along with the unusual C-acylated side product, identified as 6-acetyl-1,7-dihydroxy-3-methylcarbazole (**9**) by PMR spectroscopy. **9** was selectively benzylated ($C_6H_5CH_2Cl/NaHCO_3/NaI$/acetone) to furnish the 7-benzyloxy derivative (**11**) instead of the desired 1-benzyloxy compound (**10**). Methylation (MeI/K_2CO_3/acetone) of **11** followed by debenzylation using NaOEt and 10% Pd-C in ethanol afforded 1-methoxy-3-methyl-7-hydroxycarbazole (**8**), which in turn was found to be different from **7** (m.p., TLC, IR and PMR) and thus indirectly indicated that the benzyl group in **11** was attached to 7-hydroxy function.

In another approach the synthesis of **10** was attempted from 7-acetoxy-1-hydroxy-3-methylcarbazole (**13**). For this **4** was demethylated with HBr (48%) to furnish 7-hydroxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**3**). Acetylation of **3** gave the 7-acetoxy derivative (**5**), which on aromatisation with 10% Pd-C in diphenyl ether furnished a mixture of five compounds, viz. **6** and **12** to **15**, which were separated by column chromatography over silica gel. In order to establish the position of acetoxy group in the monoacetyl carbazoles (**13**) and (**14**), they were subjected to methylation followed by deacetylation to furnish **8** and **7** respectively. Formation of **7** from **14** confirmed that the acetyl group in **14** was attached to 1-hydroxy group and that in **13** at 7-hydroxy function.

†CDRI Communication No. 3769

Various attempts for selective benzylation of **13** proved abortive due to the formation of complex reaction mixtures, which were found difficult to separate. Yet in another experiment it was found that the condensation of **14** with 2-methyl-3-buten-2-ol in the presence of BF_3 etherate gave a mixture from which the desired 1-acetoxy-7-hydroxy-3-methyl-8-(3,3-dimethylallyl)carbazole (**16**) and compounds (**17** to **21**) could be isolated by column chromatography over silica gel. In a modified procedure **14** was obtained in good yield by direct acetylation of **6** using Ac_2O in pyridine.

Methylation of (Me_2SO_4/K_2CO_3/acetone) of **16** resulted in 1-acetoxy-7-methoxy-3-methyl-8-(3,3-dimethylallyl)-carbazole (**22**), which on hydrolysis with NaOMe in methanol at room temperature afforded murrayafoline-B (**1**). The pyridinium chlorochromate (PCC) oxidation of **1** in dichloromethane afforded murrayaquinone-B (**2**), which was found identical with the natural product (full spectroscopic data). To the best of our knowledge this is the first report of synthesis of desired quinone by PCC oxidation of a substituted phenol.

Experimental Procedure

All m.ps are uncorrected. The IR spectra were recorded on a beckman Acculab-1 or Perkin-Elmer 577 grating instrument, UV spectra on a Hitachi model 320 spectrophotometer and PMR spectra either on a Varian EM-360L or Perkin-Elmer R-32 or Brucker WM-400 spectrometer using TMS as an internal standard. The chemical shift values are expressed in δ units. The mass spectra were run on a Jeol D-300 mass spectrometer fitted with all glass direct inlet system. The TLC and PLC were carried on Merck silica gel G. All the compounds reported herein gave satisfactory C, H and N analyses.

1-*Hydroxy*-7- *methoxy*-3-*methylcarbazole* (7)

A mixture of 7-methoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**4**, 8 g), diphenyl ether (35 ml) and 10% Pd-C (2 g) was refluxed for 1.5 hr, cooled, extracted with 10% aq NaOH (3 × 50 ml) and the alkaline extract washed with ether. The aqueous layer was acidified with 1*N* HCl, extracted with ether (3 × 50 ml), the ethereal layer washed with water (2 × 100 ml), dried (Na_2SO_4) and evaporated to afford a residue, which was chromatographed over a column of silica gel to give **7** (6 g), m.p. 217-19°, IR: 3460, 3340, 1610 and 1575 cm^{-1}; UV: 240, 254 (sh), 300, 322 (sh) and 332 (sh) nm; PMR (acetone-d_6): 2.42 (*s*, 3H, Ar-CH_3), 3.82 (*s*, 3H, $-OCH_3$), 6.65 (*d*, 1H, H-2 or H-8, J = 2.0 Hz), 6.75 (*dd*, 1H, H-6, J = 8.0 and 2.0 Hz), 6.95 (*d*, 1H, H-2 or H-8, J = 2.0 Hz), 7.36 (*d*, 1H, H-4, J = 2.0 Hz) and 7.84 (*dd*, 1H, H-5, J = 8.0 and 2.0 Hz); MS: *m/z* 227 (M^+) and 212.

1,7-*Dihydroxy*-3-*methylcarbazole* (**6**)

A solution of **7** (4 g) in gl AcOH (25 ml) and HBr (20 ml, 48%) was refluxed at 135-40° for 4 hr, cooled, diluted with water and extracted with ether (4 × 50 ml). The ethereal layer was washed with water, dried (Na_2SO_4), the solvent removed and the residue chromatographed over a column of silica gel using chloroform-methanol (99:1) as eluant to afford 6-*acetyl*-1,7-*dihydroxy*-3-*methyl-carbazole* (**9**), (500 mg), m.p. 295-97° (d); IR: 3320, 1640, and 1590 cm^{-1}; UV: 220 (sh), 243, 275, 296 and 360 nm; PMR (acetone-d_6 + DMSO-d_6): 2.30 (*s*, 3H, Ar-CH_3), 2.63 (*s*, 3H, $-COCH_3$), 6.60 (*s*, 1H, H-8), 6.70 (*d*, 1H, H-2, J = 2.0 Hz), 7.25 (*d*, 1H, H-4, J = 2.0 Hz), 7.40 (*bs*, 1H, $-NH$) and 8.50 (*s*, 1H, H-5); MS: *m/z* 255 (M^+), 240 and 212. Further elution with chloroform-methanol (95:5) gave **6** (2.5 g), m.p. 235-38° ($CHCl_3$ + MeOH) (d); IR: 3420, 3380, 1615 and 1580 cm^{-1}; UV: 216 (sh), 242, 252 (sh), 300, 320 (sh) and 334 (sh) nm; PMR(acetone-d_6): 2.25 (*s*, 3H, Ar-CH_3), 6.25 (*dd*, 1H, H-6, J = 8.0 and 2.0 Hz), 6.55 (*d*, 1H, H-8, J = 2.0 Hz), 6.85 (*s*, 1H, H-2), 7.40 (*d*, 1H, H-5, J = 8.0 Hz), 7.55 (*s*, 1H, H-4) and 9.30 (*bs*, 1H, $-NH$); MS: *m/z* 213 (M^+).

1-*Hydroxy*-7-*benzyloxy*-3-*methylcarbazole* (**11**)

A mixture containing **6** (500 mg), $NaHCO_3$ (3 g), $C_6H_5CH_2Cl$ (0.25 ml) and NaI (200 mg) was refluxed for 24 hr. It was cooled, filtered and solvent removed to give a residue, which was purified through PLC ($CHCl_3$-MeOH; 98:2) to afford **11** (80 mg), m.p. 180-85°; IR: 3400, 1620 and 1580 cm^{-1}; PMR($CDCl_3$): 2.40 (*s*, 3H, Ar-CH_3), 5.10 (*s*, 2H, $-OCH_2Ph$), 6.67 (*s*, 1H, H-2), 6.80 (*dd*, 1H, H-6, J = 8.0 and 2.0 Hz), 6.90 (*d*, 1H, H-8, J = 2.0 Hz), 7.10 to 7.50 (*m*, 6H, H-4 and $-C_6H_5$) and 7.70 (*d*, 1H, H-5, J = 8.0 Hz); MS: *m/z* 303 (M^+) and 212 ($M^+ - 91$).

7-*Hydroxy*-1-*methoxy*-3-*methylcarbazole* (**8**)

Method A: A mixture of **11** (50 mg), MeI (1 ml) and K_2CO_3 (200 mg) in acetone (50 ml) was refluxed for 4 hr. After usual work-up the residue was diluted with dry ethanol (20 ml), 10% Pd-C (25 mg) and NaOEt (25 mg) were added and the solution refluxed for another 15 min. It was filtered, concentrated, diluted with water and acidified to give a residue which was purified through PLC ($CHCl_3$-MeOH; 97:3) to afford **8** (12 mg), m.p. 150-52°; IR: 3380, 1615 and 1580 cm^{-1}; PMR(acetone-d_6): 2.44 (*s*, 3H, Ar-CH_3), 3.88 (*s*, 3H, OCH_3), 6.60 (*s*, 1H, H-2), 6.70 (*dd*, 1H, H-6, J = 8.0 and 2.0 Hz), 6.90 (*d*, 1H, H-8, J = 2.0 Hz), 7.40 (*s*, 1H, H-4) and 7.75 (*d*, 1H, H-5, J = 8.0 Hz); MS: *m/z* 227 (M^+).

Method B: A mixture of **13** (50 mg), K_2CO_3 (50 mg) and Me_2SO_4 (0.2 ml) was stirred at room temperature for 3 hr. After usual work-up the residue was dissolved in MeOH and NaOMe (25 mg) was added. After 10 min the solvent was removed, the residue diluted with

water and acidified with conc HCl. The precipitated material was filtered and dried (Na_2SO_4) to afford **8** (25 mg), identical with the product obtained by method-A (m.p., TLC, IR and PMR).

7-Hydroxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**3**)

A mixture of **4** (5 g), HBr (40 ml, 48%) and gl AcOH (40 ml) was refluxed for 6 hr, cooled, the precipitate filtered, washed with 5% aq $NaHCO_3$ (50 ml), water and dried (Na_2SO_4) to afford **3** (4 g), m.p. 275-78° (EtOAc); IR: 3325, 3210 and 1590 cm^{-1}; UV: 204, 214, 236, 258 and 335 nm; PMR(TFA): 1.10 (*bs*, 3H, $-CH_3$), 2.30-3.10 (*m*, 5H, $-CH_2-CH-CH_2-$), 6.75 (*dd*, 1H, H-6, $J=8.0$ and 2.0 Hz), 7.02 (*d*, 1H, H-8, $J=2.0$ Hz) and 7.55 (*d*, 1H, H-5, $J=8.0$ Hz); MS: *m/z* 215 (M^+).

7-Acetoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**5**)

A solution of **3** (5 g), pyridine (10 ml) and Ac_2O (20 ml) was refluxed for 1 hr. Usual work-up gave **5** (5 g), m.p. 249-51° (acetone); IR: 3320, 1730, 1640 and 1610 cm^{-1}; UV: 206, 236 and 312 nm; PMR(DMSO-d_6): 1.05 (*bs*, 3H, $-CH_3$), 2.32 (*s*, 3H, $-OCOCH_3$), 2.40-3.15 (*m*, 5H, $-CH_2-CH-CH_2-$), 6.55 (*dd*, 1H, H-6, $J=8.0$ Hz and 2.0 Hz), 6.67 (*d*, 1H, H-8, $J=2.0$ Hz), 7.35 (*d*, 1H, H-5, $J=8.0$ Hz) and 11.6 (*bs*, 1H, $-NH$); MS: *m/z* 257 (M^+) and 215 (M^+-42).

1-Acetoxy-7-hydroxy-3-methylcarbazole (**14**)

Method A: A mixture of **5** (5g), 10% Pd-C (1.25 g) and diphenyl ether (20 ml) was refluxed on an oil-bath for 90 min, cooled, diluted with ether (250 ml) and filtered. The filterate was evaporated to furnish an oil which was diluted with hexane (500 ml). The precipitate was filtered and dried (Na_2SO_4) to give a crude product (4 g), which was chromatographed over a column of silica gel using chloroform with increasing amounts of methanol as eluent to afford five compounds (**6** and **12** to **15**). Elution with chloroform gave *1,7-diacetoxy-3-methylcarbazole* (**15**) (350 mg), m.p. 174-76° ($CHCl_3$ + MeOH); IR: 3305, 1750, 1725 and 1605 cm^{-1}; UV: 236, 260 (sh), 292, 324 and 338 (sh) nm; PMR ($CDCl_3$ + acetone-d_6): 2.23 and 2.27 (each *s*, 6H, 2 × $-OCOCH_3$), 2.40 (*s*, 3H, Ar-CH_3), 6.80 (*dd*, 1H, H-6, $J=8.0$ and 2.0 Hz), 6.95 (*s*, 1H, H-2), 7.05 (*d*, 1H, H-8, $J=2.0$ Hz), 7.55 (*s*, 1H, H-4), 7.8 (*d*, 1H, H-5, $J=8.0$ Hz) and 9.70 (*bs*, 1H, $-NH$). MS: *m/z* 297 (M^+), 255 (M^+-42) and 213 (M^+-84). Elution with $CHCl_3$-MeOH (99.75:0.25) afforded *7-acetoxy-3-methylcarbazole* (**12**) (400 mg), m.p. 270-73°; IR: 3380, 1740 and 1600 cm^{-1}; UV: 224, 240, 292, 326 and 340 (sh) nm; PMR(acetone-d_6): 2.20 (*s*, 3H, $-OCOCH_3$), 2.40 (*s*, 3H, Ar-CH_3), 6.80 (*dd*, 1H, H-6, $J=8.0$ and 2.0 Hz), 7.00 to 7.35 (*m*, 3H, H-1, H-2 and H-8), 7.78 (*s*, 1H, H-4) and 7.95 (*d*, 1H, H-5, $J=8.0$ Hz); MS: *m/z* 239 (M^+) and 197 (M^+-42). Elution with $CHCl_3$ – MeOH (99.5:0.5) furnished *7-acetoxy-1-hydroxy-3-methylcarbazole* (**13**) (1.25 g), m.p. 182-84° ($CHCl_3$); IR: 3400, 3360, 1690 and 1585 cm^{-1}; UV: 226, 234, 294, 326 and 340 (sh) nm; PMR($CDCl_3$): 2.28 (*s*, 3H, $-OCOCH_3$), 2.40 (*s*, 3H, Ar$-CH_3$), 6.67 (*s*, 1H, H-2), 6.83 (*dd*, 1H, H-6, $J=8.0$ and 2.0 Hz), 7.14 (*d*, 1H, H-8, $J=2.0$ Hz), 7.30 (*s*, 1H, H-4) and 7.85 (*d*, 1H, H-5, $J=8.0$ Hz); MS: *m/z* 355 (M^+) and 212 (M^+-42). Elution with $CHCl_3$ – MeOH (99.25:0.75) afforded *1-acetoxy-7-hydroxy-3-methylcarbazole* (**14**) (400 mg), m.p. 225-27° ($CHCl_3$); IR: 3400, 3320, 1720, 1635 and 1610 cm^{-1}; UV: 214, 238, 256 (sh), 302, 320 (sh), 332 (sh) and 346 (sh) nm; PMR(acetone-d_6): 2.25 (*s*, 3H, $-OCOCH_3$), 2.40 (*s*, 3H, Ar$-CH_3$), 6.65 (*dd*, 1H, H-6, $J=8.0$ and 2.0 Hz), 6.82 (*s*, 1H, H-2), 6.85 (*d*, 1H, H-8, $J=2.0$ Hz), 7.54 (*s*, 1H, H-4), 7.75 (*d*, 1H, H-5, $J=8.0$ Hz) and 9.90 (*bs*, 1H, $-NH$); MS: *m/z* 255 (M^+) and 212 (M^+-42). Further elution with $CHCl_3$ – MeOH (96:4) gave *1,7-dihydroxy-3-methylcarbazole* (**6**) (800 mg).

Method B: A solution of **6** (2 g), Ac_2O (0.4 ml) and pyridine (5 ml) was stirred at 125-30° for 6 hr. Pyridine was removed *in vacuo* and the residue chromatographed over a column of silica gel. Elution with chloroform gave **15** (50 mg). Further elution with chloroform-methanol (99.5:0.5) afforded **13** (200 mg) and **14** (950 mg). The starting **6** (350 mg) was also recovered after eluting the column with chloroform-methanol (96:4).

1-Acetoxy-7-hydroxy-3-methyl-8-(1,1-dimethylallyl)carbazole (**16**)

To a solution of **14** (500 mg) in dry dioxane (25 ml) was added BF_3 etherate (0.5 ml) and the mixture stirred at room temperature for 10 min. To this solution, 2-methyl-3-buten-2-ol (0.5 ml) was added and stirring continued for another 1 hr. It was then diluted with water (150 ml), extracted with ether (3 × 50 ml), the ethereal layer washed with water, dried (Na_2SO_4), concentrated and the residue chromatographed over a column of silica gel. Elution with $CHCl_3$-hexane (80:20) gave *1-acetoxy-7-hdydroxy-3-methyl-6,8-bis(3,3-dimethylallyl)carbazole* (**21**) as an oil (30 mg); IR: 3420, 1740 and 1620 cm^{-1}; UV: 220, 243, 256 (sh), 300, 304 (sh) and 338 (sh) nm; PMR($CDCl_3$): 1.76 and 1.84 [each *s*, 12H, 2 × $=C(CH_3)_2$], 2.34 (*s*, 3H, $-OCOCH_3$), 2.45 (*s*, 3H, Ar$-CH_3$), 3.50 (*m*, 4H, 2 × Ar$-CH_2-$), 5.30 (*m*, 2H, 2 × CH$=CMe_2$), 6.85 (*s*, 1H, H-2), 7.50 (*s*, 1H, H-4) and 7.80 (*s*, 1H, H-5); MS: *m/z* 391 (M^+). Elution with $CHCl_3$-hexane (90:10) afforded *1-acetoxy-3-methyl-6-(3,3-dimethylallyl)-7-(3,3-dimethylallyloxy)carbazole* (**20**) (35 mg), m.p. 144-46 ($CHCl_3$ + hexane); IR: 3400, 1720, 1630 and 1615

cm^{-1}; UV: 218, 242, 275 (sh), 305, 328 (sh) and 340 (sh) nm; PMR($CDCl_3$): 1.54 and 1.74 [each *s*, 12H, 2 × $=C(CH_3)_2$], 2.25 (*s*, 3H, $-OCOCH_3$), 2.40 (*s*, 3H, Ar $-CH_3$), 3.35 (*d*, 2H, Ar$-CH_2-$, $J=7.0$ Hz), 4.70 (*d*, 2H, $-OCH_2-$, $J=5.0$ Hz), 5.20 (*m*, 2H, 2 × $-CH=CMe_2$), 6.56 (*s*, 1H, H-8), 6.78 (*s*, 1H, H-2), 7.50 (*s*, 1H, H-4), 7.58 (*s*, 1H, H-5); MS: *m/z* 391 (M^+). Elution with $CHCl_3$ furnished 1-*acetoxy*-3-*methyl*-7-(3,3-*dimethylallyloxy*)-8-(3,3-*dimethylallyl*)*carbazole* (**19**) as an oil (40 mg), IR: 3400, 1735 and 1615 cm^{-1}; UV: 220, 244, 256 (sh), 302, 324 (sh), 332 (sh) and 356 (sh) nm; PMR($CDCl_3$): 1.65, 1.70, 1.73 and 1.85 [each *s*, 12H, 2 × $=C(CH_3)_2$], 2.25 (*s*, 2H, $-OCOCH_3$), 2.45 (*s*, 3H, Ar$-CH_3$), 3.62 (*d*, 2H, Ar$-CH_2-$, $J=7.0$ Hz), 4.90 (*d*, 2H, $-OCH_2-$, $J=5.0$ Hz), 5.25 (*m*, 2H, 2 × $-CH=CMe_2$), 6.65 (*d*, 1H, H-6, $J=8.0$ Hz), 6.78 (*s*, 1H, H-2), 7.52 (*s*, 1H, H-4) and 7.65 (*d*, 1H, H-5, $J=8.0$ Hz); MS: *m/z* 391 (M^+). Elution with $CHCl_3$ – MeOH (99.75:0.25) gave 1-*acetoxy*-7-*hydvoxy*-3-*methyl*-8-(3,3-*dimethylallyl*)*carbazole* (**16**) (80 mg), m.p. 164-65° ($CHCl_3$ + hexane); IR: 3420, 1740 and 1620 cm^{-1}; UV: 222, 243, 256 (sh), 302, 318 (sh) and 332 (sh) nm; PMR($CDCl_3$): 1.72 and 1.81 [each *s*, 6H, $=C(CH_3)_2$], 2.33 (*s*, 3H, $-OCOCH_3$), 2.42 (*s*, 3H, Ar$-CH_3$), 3.48 (*d*, 2H, Ar$-CH_2-$, $J=7.0$ Hz), 5.30 (*m*, 1H, $-CH=CMe_2$), 6.60 (*d*, 1H, H-6, $J=8.0$ Hz), 6.85 (*s*, 1H, H-2), 7.50 (*s*, 1H, H-4), 7.56 (*d*, 1H, H-5, $J=8.0$ Hz) and 7.84 (*bs*, 1H, –NH); MS: *m/z* 323 (M^+). Elution with $CHCl_3$ – MeOH (99.5:0.5) afforded 1-*acetoxy*-3-*methyl*-7-(3,3-*dimethylallyloxy*)-*carbazole* (**17**) (125 mg), m.p. 161-63° ($CHCl_3$): IR: 3400, 1755, 1720, 1625 and 1605 cm^{-1}; UV: 218, 240, 260 (sh), 304, 325 (sh) and 340 (sh) nm; PMR($CDCl_3$): 1.60 and 1.75 [each *s*, 6H, $=C(CH_3)_2$], 2.20 (*s*, 3H, $-OCOCH_3$), 2.35 (*s*, 3H, Ar$-CH_3$), 4.75 (*d*, 2H, $-OCH_2-$, $J=5.0$ Hz), 5.10 (*m*, 1H, $-CH=CMe_2$), 6.65 (*dd*, 1H, H-6, $J=8.0$ and 2.0 Hz), 6.70 (*d*, 1H, H-8, $J=2.0$ Hz), 6.80 (*s*, 1H, H-2), 7.55 (*s*, 1H, H-4) and 7.75 (*d*, 1H, H-5, $J=8.0$ Hz); MS: *m/z* 323 (M^+). Elution with $CHCl_3$ – MeOH (99:1) furnished 1-*acetoxy*-7-*hydroxy*-3-*methyl*-6-(3,3-*dimethylallyl*)*carbazole* (**18**) (30 mg), m.p. 155-57° ($CHCl_3$); IR: 3400, 1740 and 1635 cm^{-1}; UV: 214, 238, 256 (sh), 304, 322 (sh) and 336 (sh) nm; PMR($CDCl_3$): 1.70 [*s*, 6H, $=C(CH_3)_2$], 2.25 (*s*, 3H, $-OCOCH_3$), 2.36 (*s*, 3H, Ar$-CH_3$), 3.35 (*d*, 2H, Ar$-CH_2-$, $J=7.0$ Hz), 5.30 (*m*, 1H, $-CH=CMe_2$), 6.56 (*s*, 1H, H-8), 6.82 (*s*, 1H, H-2), 7.46 (*s*, 1H, H-4), 7.52 (*s*, 1H, H-5) and 7.75 (*s*, 1H, –NH); MS: *m/z* 323 (M^+).

1-Acetoxy-7-methoxy-3-methyl-8-(3,3-dimethylallyl)carbazole (**22**)

A mixture of **16** (50 mg), Me_2SO_4 (0.05 ml) and K_2CO_3 (100 mg) was stirred at room temperature for 4 hr. Usual work-up afforded **22** (35 mg), m.p. 127-29° ($CHCl_3$ + hexane); IR: 3360, 1735 and 1610 cm^{-1}; UV: 220, 244, 254 (sh), 300, 320 (sh) and 336 (sh) nm; PMR($CDCl_3$): 1.72 and 1.82 [each *s*, 6H, $=C(CH_3)_2$], 2.32 (*s*, 3H, $-OCOCH_3$), 2.42 (*s*, 3H, Ar$-CH_3$), 3.54 (*d*, 2H, Ar$-CH_2-$, $J=7.0$ Hz), 3.82 (*s*, 3H, $-OCH_3$), 5.26 (*m*, 1H, $-CH=CMe_2$), 6.75 (*d*, 1H, H-6, $J=8.0$ Hz), 6.85 (*d*, 1H, H-2, $J=2.0$ Hz), 7.50 (*d*, 1H, H-4, $J=2.0$ Hz) and 7.65 (*d*, 1H, H-5, $J=8.0$ Hz); MS: *m/z* 337 (M^+).

Murrayafoline-B (**1**)

A solution of **22** (30 mg) in dry methanol (20 ml) was treated with NaOMe (30 mg). After 15 min, the solvent was removed, the residue diluted with water and acidified with *N* HCl. The precipitate was extracted with ethyl acetate, washed with water, dried (Na_2SO_4), concentrated and the residue on PLC ($CHCl_3$ – MeOH; 99:1) purification gave murrayafoline-B (20 mg), m.p. 212-14° ($CHCl_3$): IR: 3400, 1640, 1620, and 1590 cm^{-1}; UV: 230 (sh), 246, 256 (sh), 300, 325 (sh) and 338 (sh) nm; PMR($CDCl_3$): 1.67 and 1.82 [each *s*, 6H, $=C(CH_3)_2$], 2.38 (*s*, 3H, Ar$-CH_3$), 3.55 (*d*, 2H, Ar$-CH_2-$, $J=7.0$ Hz), 3.83 (*s*, 3H, $-OCH_3$), 5.25 (*m*, 1H, $-CH=CMe_2$), 6.50 (*s*, 1H, H-2), 6.75 (*d*, 1H, H-6, $J=8.0$ Hz), 7.30 (*s*, 1H, H-4), 7.70 (*d*, 1H, H-5, $J=8.0$ Hz) and 7.90 (*bs*, 1H, –NH); MS: *m/z* 295 (M^+) and 280 ($M^+ - 15$).

Murrayaquinone-B (**2**)

To a well stirred solution of PCC (15 mg) in dry dichloromethane (10 ml), murrayafoline-B (15 mg) was added in one portion. After few seconds dry ether (100 ml) was added and the supernatant liquid was decanted from the black gum. It was passed through a short column of florisil and removal of solvent furnished murrayaquinone-B (5 mg), m.p. 217-19° (lit.[1], m.p. 221-23°); IR: 3275, 1655, 1635 and 1605 cm^{-1}; UV: 210, 230, 264, 310 and 405 (br) nm; PMR(acetone-d_6): 1.67 and 1.87 [each *s*, 6H, $=C(CH_3)_2$], 2.05 (*d*, 3H, $-CH_3$, $J=1.5$ Hz), 3.60 (*d*, 2H, Ar$-CH_2-$, $J=7.0$ Hz), 3.85 (*s*, 3H, $-OCH_3$), 5.20 (*m*, 1H, $-CH=CMe_2$), 6.40 (*q*, 1H, H-2, $J=1.5$ Hz), 7.05 (*d*, 1H, H-6, $J=8.0$ Hz) and 7.90 (*d*, 1H, H-5, $J=8.0$ Hz); MS: *m/z* 309 (M^+), 294 ($M^+ - 15$), 254 ($M^+ - 55$) and 241 ($M^+ - 68$).

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Novel Pyrones from *Hypericum mysorense* Heyne†‡

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The aerial parts of *Hypericum mysorense* Heyne afford two new pyrones, characterised as 3-(1,1-dimethyl-2-propenyl)-6-phenyl-2,4(3*H*)-dioxopyran (**6**) and 3(1,1-dimethyl-2-propenyl)-2-methoxy-6-phenyl-4*H*-pyran-4-one (**8**). The structures have been assigned on the basis of physical data and confirmed by syntheses.

As a part of our phytochemical study on plants showing promising antifungal activity[1], the aerial parts of *Hypericum mysorense* Heyne (Hypericaceae) were examined. The 95% ethanolic extract on concentration followed by dilution with water, extraction with hexane and ethyl acetate indicated that antifungal activity was confined only in ethyl acetate fraction. This fraction on column chromatography over silica gel yielded two novel pyrones (A) and (B).

Pyrone-A was purified as an oil and it analysed for $C_{17}H_{18}O_3$ (M^+, *m/z* 270). That (A) had a 6-phenyl-γ-pyrone nucleus[2], was evident from characteristic UV (230 and 270 nm) and IR bands (1660 cm^{-1}). The PMR (90 MHz) spectrum (see Experimental) clearly indicated the presence of 1,1-dimethyl-2-propenyl side chain[3,4], enolic methoxyl (*s*, 3H, δ 3.95) and five aromatic protons (monosubstituted phenyl) as a 3+2 pattern (δ 7.30 and 7.70 respectively). The C-5 proton of the pyrone nucleus[3,4] appeared as a sharp singlet at δ 6.45. The mass spectral fragmentation data indicated the attachment of phenyl ring to C-6 position of pyrone nucleus and the appearance of the strong ions at *m/z* 105 ($PhCO^+$) and 77 $(Ph)^+$ confirmed that phenyl ring was monosubstituted, a fact corroborated by PMR spectrum. The attachment of methoxyl group at C-2 in γ-pyrone was in agreement with biogenetic considerations[5].

The point of attachment of 1,1-dimethyl-2-propenyl side chain at C-3 of pyrone nucleus was confirmed by synthesis.

All these facts supported the structure of compound (A) as 3-(1,1-dimethyl-2-propenyl)-2-methoxy-6-phenyl-4*H*-pyran-4-one (**8**) which is in agreement with its CMR data.

Compound (B) was also obtained as an oil and it analysed for $C_{16}H_{16}O_3$ (M^+, *m/z* 256). The PMR and CMR data indicated it to possess sixteen carbons and same number of protons. In CMR spectrum, two peaks in the range of 180-200 ppm, originating from two carbonyl carbons, were discernible. The UV data showed bands at 250 and 310 nm, a characteristic feature of α-pyrone nuclueus[2]. This was also supported by the appearance of a strong peak at 1740 cm^{-1} in the IR spectrum. An additional broad band at 1610 cm^{-1} was due to γ-pyrone carbonyl function[2].

The PMR spectrum clearly showed the presence of monosubstituted phenyl ring and one 1,1-dimethyl-2-propenyl grouping, the chemical shifts and coupling constants values were similar to those obtained for compound (A). The singlet at δ 2.35 was due to C-3 proton flanked by 2,4-dicarbonyl system. Another singlet at δ 6.10 was assignmd to the C-5 proton of pyranone nucleus.

The attachment of the inverted prenyl chain at C-3 of the pyranone nucleus was based on PMR data and confirmed by CMR spectroscopy (see Experimental). Compound (B) was, therefore, assigned the structure as 3-(1,1-dimethyl-2-propenyl)-6-phenyl-2,4(3*H*)-dioxopyran (**6**).

For the synthesis of **6** and **8** ethyl acetoacetate (**1**) was condensed with ethyl benzoate (**2**) in the presence of sodium hydride (Scheme 1) to furnish 5-phenyl-3,5-dioxopentanoic acid (**3**) in 40% yield instead of the diketo ester. **3** was cyclised to the lactone (**4**) with polyphosphoric acid. Lactone (**4**) was condensed with 3,3-dimethyl-2-propenyl bromide in the presence of thallium ethoxide, to give 4-(3,3-dimethyl-2-propenyloxy)-6-phenylpyran-2-one (**5**). When **5** was heated in DMSO at 120°, the Claisen rearrangemmnt on 3,3-dimethyl-2-propenyl group occurred leading to 3-(1,1-dimethyl-2-propenyl)-6-phenyl-2,4(3*H*)-dioxopyran (**6**), which was found to be identical (m.p., UV, IR and PMR) with the natural product. The pyranone (**6**) when treated with diazomethane in ether, afforded a mixture of two compounds. These were separated by column chromatography and one of them was identical with natural **8** while the other was characterised as 3-(1,1-dimethyl-2-propenyl)-4-

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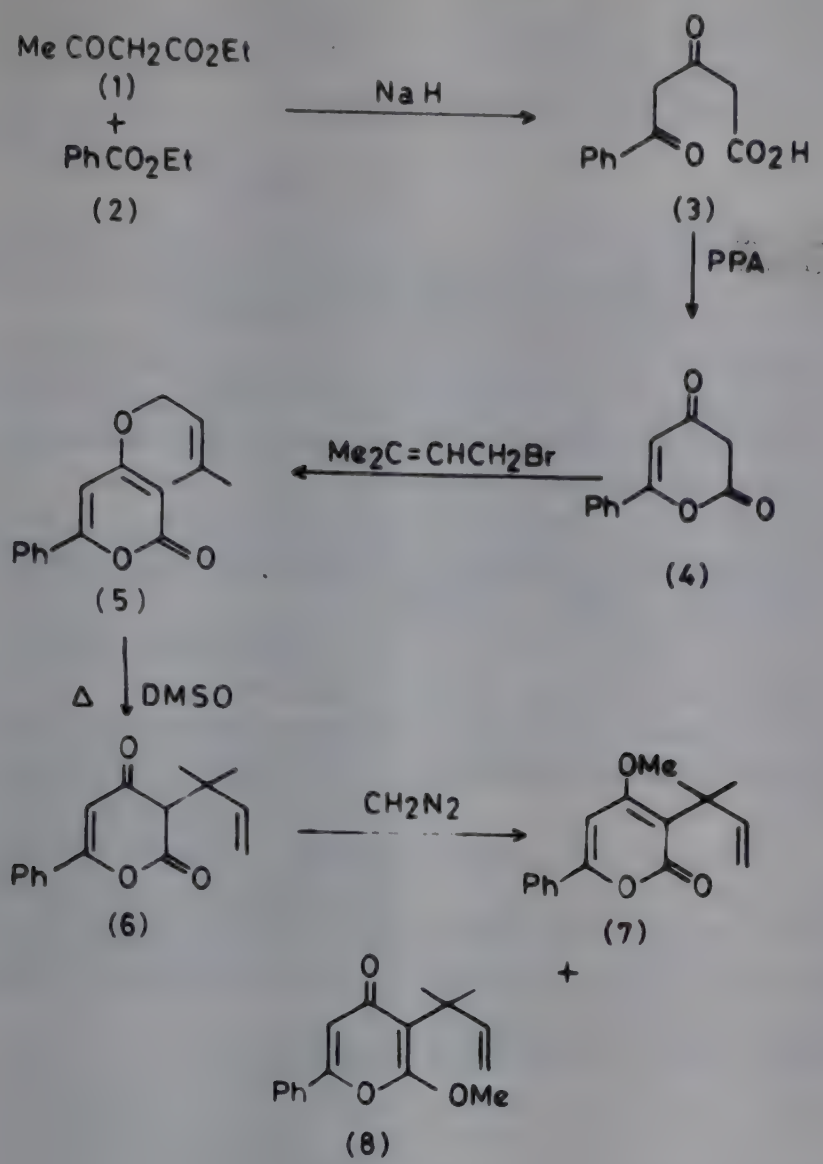
‡Part XV in the series *Studies in medicinal plants*. For Part XIV see Prasad A V K, Kapil R S & Popli S P, *Indian J Chem*, **24B** (1985) 236.



Scheme 1

methoxy-6-phenyl-2*H*-pyran-2-one (7). Compound (7) has earlier been reported by us from *H. mysorense*[7].

Experimental Procedure

Unless otherwise stated IR spectra (ν_{max} in cm^{-1}) were measured on a Perkin-Elmer 157 instrument, UV data (λ_{max} in nm) in MeOH on a Hitachi 320 instrument and PMR spectra in $CDCl_3$ either at 90 MHz (R-32) or 80 MHz (CFT-20) instrument. The CMR spectra were recorded on a 20 MHz instrument, chemical shifts are expressed in δ value downfield from TMS (internal standard). Mass spectra were taken at 70 eV on a Jeol JMS-D300 spectrometer.

Isolation of constituents

Finely powdered, air-dried whole plant (excluding roots) of *H. mysorense* (18 kg) was percolated with 95% ethanol (50 litres). The ethanolic extract was concentrated under reduced pressure, the crude concentrate (2.5 kg) dissolved in water (2 litres) and defatted with hexane (3 × 1 litre) and the aqueous layer concentrated. The residue was fractionated with ethyl acetate (3 × 1 litre) and the organic extract concentrated to yield a residue (450 g). A part of this material (100 g) on column chromatography over silica gel (2 kg) in hexane-benzene gave a mixture of compounds, which on repeated column chromatography provided compounds (A) (800 mg) and (B) (1 g). Compound (A) was characterised as 3-(1,1-dimethyl-2-propenyl)-2-methoxy-6-phenyl-4*H*-pyran-4-one (**8**): UV(MeOH): 230 and 270; IR($CHCl_3$): 1660, 1580, 1480, 1380, 1340, 1260 and 760; PMR: 1.40 (*s*, 6H, *gem*-dimethyl), 3.95 (*s*, 3H, OCH_3), 4.6 to 4.9 (*dd*, 2H, $-CH=CH_2$), 5.95-6.30 (*d*, 1H, $-CH=CH_2$), 6.45 (*s*, 1H, C_5-H), 7.30 (*m*, 3H, *m*- and *p*-Ar protons) and 7.70 (*m*, 2H, *o*-Ar protons); CMR: 181.4 (C-4), 162.0 (C-2), 157.0 (C-6), 148.2 (C-4″), 130.0 (C-1′), 130.0 (C-4′), 129.0 (C-2′), 129.0 (C-6′), 125.0 (C-3′), 125.0 (C-5′), 111.6 (C-3), 111.1 (C-5), 108.3 (C-5″), 56.0 (OMe), 38.8 (C-1″), 27.5 (C-2″) and 27.5 (C-3″); MS: *m/z* 270 (M^+), 255, 241, 105, 77 and 69.

Compound (B) was identified as 3-(1,1-dimethyl-2-propenyl)-6-phenyl-2,4(3*H*)-dioxopyran (**6**): UV(MeOH): 250 and 310; IR($CHCl_3$): 2900, 1740, 1610 (*br*), 1460, 1260, 1120, 1010 and 910; PMR: 1.12 (*s*, 6H, *gem*-dimethyl), 2.35 (*s*, 1H, COCHCO), ABX pattern for $-CH=CH_2$ system (4.95, 5.00 and 5.93), 6.10 (*s*, 1H, C_5-H), 7.45 (*m*, 3H, *m*- and *p*-Ar protons) and

7.87 (*m*, 2H, *o*-Ar protons); CMR: 193.3 (C-4), 184.6 (C-2), 147.2 (C-4′), 135.0 (C-4′), 132.0 (C-1′), 128.0 (C-2′), 128.0 (C-6′), 123.0 (C-5′), 123.0 (C-3′), 110.7 (C-5′), 98.2 (C-5), 51.2 (C-3), 29.6 (C-1″), 27.0 (C-2″) and 27.0 (C-3″); MS: *m/z* 256 (M^+).

5-Phenyl-3,5-dioxopentanoic acid (**3**)

To a stirred suspension of NaH (10.6 g) in refluxing 1,2-dimethoxyethane (200 ml) was added, during 20 min, a mixture of ethyl acetoacetate (13 g) and ethyl benzoate (24 g) in dry 1,2-dimethoxyethane (100 ml). The reaction mixture was refluxed for another 8 hr under nitrogen and the excess of solvent removed *in vacuo*. The residual paste was diluted with ether (200 ml), crushed ice (150 g) and aqueous layer separated and acidified with cold 6*N* HCl. The resulting red oil was quickly extracted with ether, washed with 5% aqueous $NaHCO_3$, the bicarbonate washings were cooled and acidified with 6*N* HCl to give crude acid (**3**). Repeated crystallisation from ether-hexane afforded pure **3** (7.9 g), m.p. 94° (lit.[6] m.p. 94.5°).

6-Phenyl-2,4-dioxopyran (**4**)

A mixture of **3** (2.1 g) and PPA (20 g) was heated for 2 hr on a steam-bath. The residual dark red solution was poured onto crushed ice to precipitate a solid which was chromatographed on silica gel to give **4** as an oil (1.7 g).

4-(3,3-Dimethyl-2-propenyloxy)-6-phenyl-2H-pyran-2-one (**5**)

The lactone (**4**, 1.5 g) was dissolved in dry benzene (10 ml) and to this solution thallium ethoxide (1 ml) was added. Immediately precipitate of thallous salt of **4** appeared, to which 3,3-dimethyl-2-propenyl bromide (2 g) in dry benzene (10 ml) was added. The reaction mixture was refluxed for 4 hr, benzene removed *in vacuo*, cooled, diluted with ice water and extracted with ether. The ether extract on concentration afforded **5** as an oil (500 mg); PMR: 1.65 (*s*, 6H, *gem*-dimethyl), 3.85 (*d*, 2H, $OCH_2HC=$), 5.35 (*t*, 1H, $OCH_2CH=$), 5.90 (*s*, 1H, C_5-H), 7.30 (*m*, 2H, *m*- and *p*-Ar protons) and 7.85 (*m*, 2H, *p*-Ar protons); MS: *m/z* 256 (M^+).

3-(1,1-Dimethyl-2-propenyl)-6-phenyl-2,4(3H)-dioxopyran (**6**)

A mixture of **5** (500 mg) in DMSO (10 ml) was heated at 120° for 6 hr. Most of DMSO was removed *in vacuo* and the residue diluted with water (50 ml). The aqueous layer was extracted with ether (3 × 30 ml), the combined organic layer washed with water, dried (Na_2SO_4) and concentrated to afford **6** (200 mg).

3-(1,1-Dimethyl-2-propenyl)-2-methoxy-6-phenyl-4H-pyran-4-one (**8**) *and 3-(1,1-dimethyl-2-propenyl-4)-4-methoxy-6-phenyl-2H-pyran-2-one* (**7**)

A solution of **6** (200 mg) in ether (30 ml) was treated with excess of diazomethane solution in ether (30 ml) and left overnight. The residue was chromatographed over silica gel to give (**8**, 60 mg) and (**7**, 120 mg), m.p. 92°. All the spectral data of synthetic **8** were found identical with those of natural material.

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Lanthanide-induced Carbon-13 NMR Shift Studies on Spirostane Sapogenins†

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The usefulness of the $Yb(fod)_3$ induced shifts for definitive carbon-13 signal assignments and conformational analysis of tigogenin, diosgenin, their acetates and hecogenin acetate has been investigated. The unanalysed ^{13}C NMR data recently reported for cannigenin, brisbagenin and pseudodiosgenin dibenzoate have been assigned.

The use of the lanthanide-induced shifts (LIS) in NMR spectroscopy is one of the most promising methods for structural analysis of organic compounds particularly in ^{13}C NMR spectroscopy of a variety of natural products[1-3]. However, steroidal sapogenins have not been investigated for LIS measurements, perhaps due to complexity of their structures. Therefore, presently we have carried out LIS experiments, using the lanthanide shift reagent (LSR), $Yb(fod)_3$ on several spirostane derivatives. To assess these studies, similar experiments have been done on androstane and cholestane derivatives.

Materials and Methods

Substrates were either available commercially or prepared as reported[2,4]. LIS measurements[5,6] were performed by adding $Yb(fod)_3$ (upto 10 ml %) in 4-7 increments (by weight) to substrate (1-2 ml) in $CDCl_3$ (1.3-1.5 ml). The ^{13}C NMR spectra were measured on a Brucker HX-90 or WH-90 NMR spectrometer at 22.63 MHz at 300 ± 5 K. LIS for different nuclei were usually obtained by least squar analysis yielding atleast correlation coefficient, $r > 0.99$ for RS > 30%; $r > 0.94$ for RS > 10%; and $r > 0.89$ for RS > 1% (RS = relative shift).

The bound shifts calculated for 1:1 LSR substrate complex for the functional carbon atom (C−α) were set to 100% and relative shifts for other carbon atoms were determined as these were of great significance in establishing stereochemical environment[2,3,5,6].

Results and Discussions

The ^{13}C NMR chemical shifts, bound shifts for 1:1 LSR-substrate complexes and relative shifts (RS)‡ for tigogenin (**3**), tigogenin acetate (**4**), diosgenin (**6**), diosgenin acetate (**7**) and hecogenin acetate (**9**), in addition to those of androstan-3β-ol (**1**), cholestan-3β-ol (**2**) and cholesterol (**5**) are given in Tables 1 and 2. It is evident that the RS values for **1** and **2** closely resemble those of **3**. The RS values of **5** and **6** show close resemblance. It can, thus, be inferred that all these compounds show a common conformational behaviour of the rings-A,-B,-C and -D. A comparison of the ^{13}C shifts for **6** and yamogenin (**8**) shows an upfield shift of C-23, hence revealing the existence of *γ-gauche* interaction in latter. Therefore, tigogenin (**3**) exists in a conformation as shown in Fig. 1.

As the ^{13}C resonance at δ 32.21 exhibit higher RS value than the resonance at 31.48, this leads to the reversal of the assignments for C-6 and C-7 as reported by Marquardt[7]. The appearance of the C-4 signal in **6** at δ 34.6 as reported by Hirai *et al.*[8] seems to be due to typographical error as C-4 resonance resonates usually at $\delta\ 43.0 \pm 0.5$ (ref. 9).

The data in Tables 1 and 2 also show that functional group at C-3, which may either be hydroxyl or

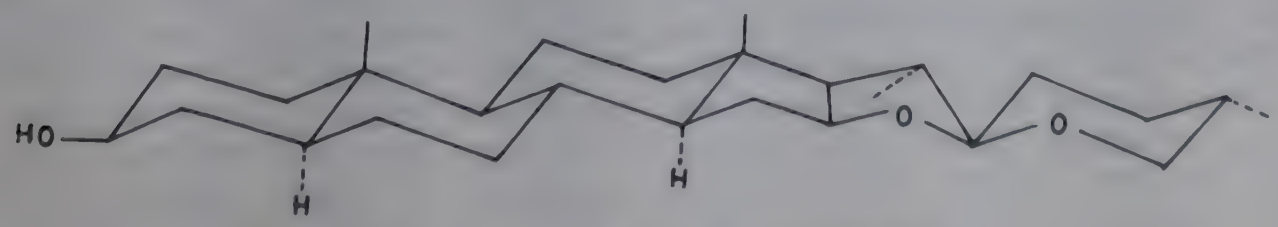
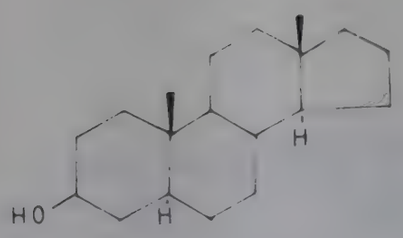


Fig. 1 – Preferred conformation of tigogenin (**3**).

† ^{13}C NMR spectral investigations: Part 11; For Part 10 see ref. 9.

‡ See footnote (a) in Tables 1 and 2.



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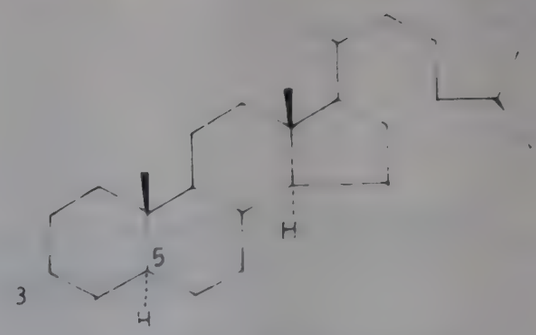
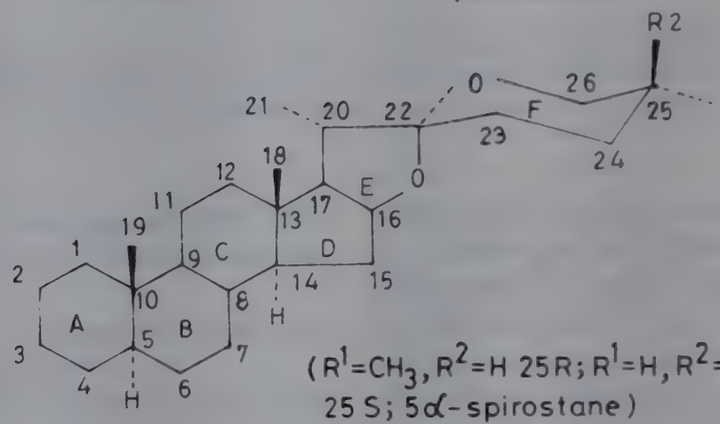


2 3β-hydroxy-5α-cholestane

5 3β-hydroxy-Δ^5-cholestane (cholesterol)



(R^1=CH_3, R^2=H 25R; R^1=H, R^2=CH_3, 25S; 5α-spirostane)

3 3β-hydroxy-(25R)-5α-spirostane (Tigogenin)

4 3β-acetoxy-(25R)-5α-spirostane (Tigogenin acetate)

6 3β-hydroxy-Δ^5-(25R)-spirostene (diosgenin)

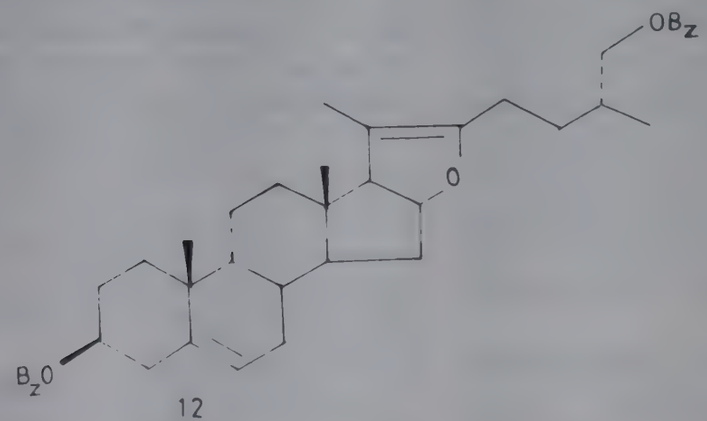
7 3β-acetoxy-Δ^5-(25R)-spirostene (diosgenin acetate)

8 3β-hydroxy-Δ^5-(25S)-spirostene (yamogenin)

9 3β-acetoxy-(25R)-5α-spirostan-12-one (Hecogenin acetate)

10 1β,3α-dihydroxy-(25R)-5α-spirostan (cannigenin)

11 1β,3β-dihydroxy-(25R)-5α-spirostan (Brisbagenin)



12

acetoxyl, provides preferred binding site for LSR complexation. The spiroketal oxygen atoms do not bind with LSR as C-22 signal does not show any remarkable shift alteration. In hecogenin acetate (**9**), Yb(fod)$_3$ is more strongly bound to the acetoxy carbonyl at C-3 than the C-12 keto group, perhaps due to the steric hindrance imposed by 18-CH_3 group. From Table 1 it is evident that RS values for C-β and C-γ for compounds with equatorial hydroxyl group at C-3 are 45 ± 1 and 19 ± 1, respectively. This criterian also holds good for acetates if one considers the LIS for C-3 which is usually 34 ± 2, equal to hundred and calculates RS values for rest of the carbon atoms.

Recently Rao and Alvarez[10] reported the unassigned ^{13}C NMR shielding data for the dihydroxylated spirostane sapogenins, namely cannigenin (**10**) and brisbagenin (**11**). These data have now been analysed (Table 2) by considering the substituent-

Table 1 – ^{13}C Chemical Shifts and Lanthanide induced ^{13}C NMR Shifts in Parentheses for Steroid Derivatives[a] (1-6)

Carbon atom	1	2	3	4	5	6
C-1	37.16(19)	37.14(19)	37.11(18)	37.44(5)	37.35(18)	37.12(19)
C-2	31.58(46)	31.52(45)	31.59(46)	29.25(16)	31.84(45)	31.58(46)
C-3	71.25(100)	71.32(100)	71.36(100)	73.34(34)	71.97(100)	71.52(100)
C-4	38.21(45)	38.28(46)	38.34(45)	36.14(15)	42.64(46)	42.24(44)
C-5	44.93(18)	45.02(19)	44.98(19)	45.36(5)	140.55(17)	140.85(18)
C-6	28.78(10)	28.83(9)	28.73(10)	28.79(3)	121.48(9)	121.36(9)
C-7	32.52(6)	32.48(5)	32.37(6)	32.24(2)	31.98(5)	32.21(6)
C-8	35.86(2)	35.69(3)	35.29(4)	35.29(1)	31.98(5)	31.48(4)
C-9	54.73(10)	54.63(8)	54.53(9)	54.53(2)	50.26(3)	50.19(8)
C-10	35.62(14)	35.57(15)	35.68(15)	35.81(4)	36.52(15)	36.68(14)
C-11	21.31(5)	21.38(3)	21.19(3)	21.19(1)	21.12(3)	20.97(3)
C-12	38.92(2)	39.88(2)	40.23(2)	40.10(1)	40.58(2)	39.89(2)
C-13	40.77(2)	42.74(2)	40.69(2)	40.69(0)	42.85(2)	40.21(2)
C-14	54.50(2)	56.50(3)	56.42(2)	56.35(0)	57.72(2)	56.57(2)
C-15	25.48(1)	24.52(2)	31.84(2)	31.85(0)	24.85(1)	31.92(2)
C-16	20.53(1)	28.82(2)	80.92(2)	80.92(0)	28.63(1)	80.78(2)
C-17	40.41(1)	57.00(2)	62.39(2)	62.39(0)	57.19(1)	62.32(2)
C-18	17.58(2)	12.64(2)	16.51(2)	16.57(0)	12.54(1)	16.35(1)
C-19	12.44(10)	12.41(10)	12.43(11)	12.74(3)	19.83(14)	19.40(12)
C-20	—	36.20(1)	41.73(2)	41.73(0)	36.52(1)	41.75(1)
C-21	—	18.95(1)	14.56(1)	14.56(0)	19.41(1)	14.54(1)
C-22	—	36.67(1)	109.32(1)	109.26(0)	37.02(0)	109.17(1)
C-23	—	24.31(1)	31.58(1)	31.52(0)	24.55(0)	31.56(1)
C-24	—	40.02(1)	28.73(1)	28.92(0)	40.36(0)	28.89(1)
C-25	—	28.27(1)	30.42(1)	30.42(0)	28.78(0)	30.37(0)
C-26	—	22.71(1)	66.94(1)	66.88(0)	23.02(0)	66.78(0)
C-27	—	22.88(1)	17.16(1)	17.16(0)	23.22(0)	17.12(0)
CO	—	—	—	170.42(100)	—	—
CH_3	—	—	—	21.35(44)	—	—

[a] In ppm relative to internal TMS (10%). LIS values are reported to the largest induced shift (S = 100%); the bound shift (ppm) for the carbon showing the largest LIS for the molar ratio Yb $(fod)_3$: substrate = 1:1; **1**, 128.2; **2**, 138.5; **3**, 148.6; **4**, 78.55; **5**, 110.8; **6**, 120.2.

Table 2 – Carbon-13 Chemical shifts and Lanthanide-induced ^{13}C NMR Shifts for Steroid Derivatives[a] (7-12)

Carbon Atom	7	8	9	10[b]	11[b]	12[c]
C-1	37.18(5)	37.2	36.33(6)	72.5	78.02	37.11
C-2	27.95(15)	31.6	27.29(18)	39.5	42.41	27.93
C-3	73.96(33)	71.7	73.18(33)	64.6	68.06	74.49
C-4	38.28(14)	42.1	33.86(16)	35.7	38.20	38.26
C-5	139.94(5)	140.8	44.52(8)	37.6	41.49	139.76
C-6	122.45(3)	120.4	28.27(3)	27.9	28.36	122.43
C-7	32.24(2)	32.0	31.52(3)	29.5	32.18	30.94
C-8	31.65(1)	31.5	34.38(3)	35.3	35.32	32.26
C-9	50.24(2)	50.1	55.38(13)	54.7	54.79	50.10
C-10	36.92(3)	36.6	36.13(7)	43.1	—	36.83
C-11	20.99(1)	20.9	37.76(17)	23.5	24.32	21.04
C-12	39.97(1)	39.8	213.79(40)	40.1	40.03	39.56
C-13	40.43(1)	40.2	55.12(13)	41.0	40.43	—
C-14	56.68(1)	56.5	55.77(5)	55.9	56.30	55.04
C-15	31.98(1)	31.8	31.52(3)	31.8	32.08	31.32
C-16	80.92(1)	80.9	79.23(6)	79.9	80.68	84.38
C-17	62.53(1)	62.0	53.69(16)	62.2	62.33	69.52
C-18	16.31(0)	16.2	16.05(9)	15.8	16.36	13.98
C-19	19.37(3)	19.4	11.89(6)	5.5	6.80	19.41
C-20	41.86(0)	42.3	42.25(6)	41.6	41.67	103.83

(*Contd.*)

Table 2—Carbon-13 Chemical Shifts and Lanthanide-induced ^{13}C NMR Shifts for Steroid Derivatives[a] (7-12)—*Contd.*

Carbon Atom	7	8	9	10[b]	11[b]	12[c]
C-21	14.56(0)	14.3	13.32(5)	14.1	14.56	11.63
C-22	109.26(0)	109.5	109.19(6)	107.9	—	151.51
C-23	31.65(0)	27.1	31.20(2)	31.4	31.40	23.28
C-24	28.99(0)	25.8	28.86(2)	29.3	28.82	30.94
C-25	30.48(0)	26.0	30.22(2)	30.8	30.30	32.24
C-26	66.94(0)	65.1	66.88(2)	65.8	66.86	69.52
C-27	17.16(0)	16.0	17.22(1)	16.6	17.14	16.83
CO	170.35(100)	—	170.48(100)	—	—	—
CH_3	21.32(43)	—	21.38(41)	—	—	—

[a] In ppm relative to internal TMS (10%). LIS values are reported to the largest induced shift (S = 100%); the bound shift (ppm) for the carbon showing the largest LIS for the molar ratio = [Yb(fod)$_3$: substrate, 1:1]: **7**, 77.63; **9**, 89.55.

[b] Calculated ^{13}C shifts C-1, C-2, C-3, C-4, C-19: for **10**, 72.4, 40.2, 64.4, 35.5, 38.4, 5.6; and for **11**, 77.1, 42.7, 69.0, 37.7, 44.1, 6.8.

[c] Other signals, 128.23, 128.28, 129.54, 129.55, 130.60, 130.90, 132.64, 132.73, 165.94, 166.58.

induced shifts[11] and by comparing these with related spirostane derivatives[9,12]. Thus, the analysis of the ^{13}C shielding data support unambiguously the proposed structures **10** and **11** which were based mainly on the results of ^1H NMR spectral analysis. During benzoylation of sterically hindered hydroxyls, using benzoyltrifluoromethane sulphonate as a mild reagent, Brown and Koreeda[13] reported the ^{13}C NMR shifts and the signal multiplicities for pseudodiosgenin dibenzoate (**12**). These shifts have now been analysed in analogy with the related compounds[4,9]. The characteristic shifts are due to the olefinic unsaturation between C-20 and C-22, thus C-20 and C-22 resonate at δ 103.83 and 151.51 respectively.

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A Diagnostic Cleavage of Aurones & Chalcones with Alkaline Hydrogen Peroxide in the Presence of Triethylbenzylammonium Chloride (TEBA)

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Aurones and chalcones on treatment with alkaline hydrogen peroxide in dioxan in the presence of triethylbenzylammonium chloride (TEBA) undergo facile cleavage to afford arylcarboxylic acids derived from rings A and B.

Epoxidation of aurones, compared to that of chalcones, requires more careful control of conditions[1,2] for getting the target compounds in moderate yields. Aurone epoxides have recently been obtained in better yields by treating aurones with hydrogen peroxide in the presence of triton-B[3]. However, aurones with a 4′-oxygenation resist epoxidation under these conditions[3].

Our study on transformation of aurones into other groups of flavonoids required aurone epoxides possising a 4′-methoxyl group. Since quaternary ammonium salts are efficient additives for the synthesis of chalcones[4] and effective phase transfer catalysts in other carbanionic reactions[5-7], it was proposed to prepare the desired aurone epoxides under modified conditions. As a typical case 6,4′-dimethoxyaurone (**2**) in dioxan was stirred with aq. NaOH (8%), triethylbenzylammonium chloride (TEBA) and hydrogen peroxide (25%) at room temperature. After the starting aurone **2** had completely reacted (TLC, 40 min), work-up of the reaction mixture gave a mixture of two products (**A** and **B**) with close R_f values on TLC. Both the products were acidic in nature as they gave a yellow colour with bromophenol blue; one of them gave a positive ferric colour. The product mixture was, therefore, methylated and subjected to preparative TLC to get the methyl esters **C** and **D**.

The compound **C** in its PMR spectrum showed two singlets at δ 3.70 and 3.78, three protons each, assignable for the protons of $-COOCH_3$ and a methoxyl group respectively. The appearance of a two-proton multiplet at δ 6.15-6.33 and a one-proton doublet at 7.52 (J = 9 Hz) indicated the aromatic substitution pattern to be 1, 2, 4.

The PMR spectrum of compound **D** also exhibited two singlets at δ 3.78 and 3.82, three protons each, indicating the presence of a $-COOCH_3$ group and a methoxyl group respectively. Two-proton doublets each at δ 6.80 (J = 9 Hz) and 7.85 (J = 9 Hz) showed *para*- disubstituted pattern in the aromatic ring.

Based on the above PMR data, compounds **C** and **D** were assigned the structures methyl 2-hydroxy-4-methoxybenzoate (**7a**) and methyl anisate (**10a**) respectively. These structures were confirmed by comparison (m.m.p., co-TLC) with authentic samples. Thus, compounds **A** and **B** were characterized as 2-hydroxy-4-methoxybenzoic acid (**7**) and anisic acid (**10**), respectively.

It thus became evident that instead of the desired epoxidation, cleavage of the aurone had occurred to give a mixture of two arylcarboxylic acids, derived from rings A and B.

The general nature of the above cleavage was proved by subjecting other aurones possessing different substitution patterns in rings A and B. In the case of aurones lacking oxygenation in ring-B, during work-up the carboxylic acid from ring-A precipitated out while benzoic acid from ring-B was obtained by salting it out from the filtrate. The reaction product was separated into individual acids by preparative TLC in the case of **3**, and in the case of **2**, **5** and **6**, conversion of the product mixtures into methyl esters was found to be essential before their resolution by preparative TLC. In the case of **5** and **6**, the reaction product on refluxing with methanol and conc. H_2SO_4 followed by preparative TLC, gave phloroglucinol dimethyl ether and methyl ester of the acid from ring-B. The phloroglucinolcarboxylic acid derivatives resulting from the initial cleavage in aurones are known to undergo ready decarboxylation under the conditions of esterification[8]. Hence, the reaction product from **5** and **6** was methylated with dimethyl

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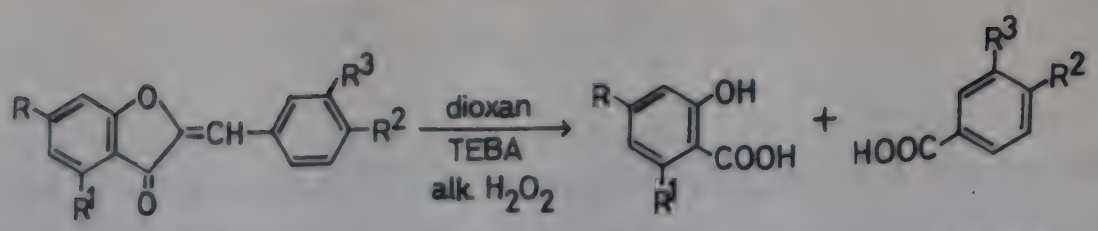
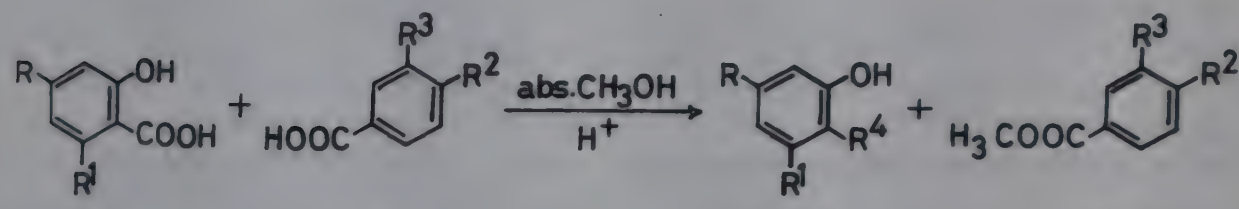


1,2,3,4,5,6 → 7,8 + 9,10,11

1 $R=OCH_3$; $R^1=R^2=R^3=H$
2 $R^1=R^3=H$; $R=R^2=OCH_3$
3 $R^1=H$; $R=R^2=R^3=OCH_3$
4 $R=R^1=OCH_3$; $R^2=R^3=H$
5 $R=R^1=R^2=OCH_3$; $R^3=H$
6 $R=R^1=R^2=R^3=OCH_3$

7 $R=OCH_3$; $R^1=H$
8 $R=R^1=OCH_3$
9 $R^2=R^3=H$
10 $R^2=OCH_3$; $R^3=H$
11 $R^2=R^3=OCH_3$



7,8 + 10,11 → 7a,8a + 10a,11a

8 + 10,11 → 8b + 10a,11a
($(CH_3)_2SO_4$, acetone, K_2CO_3)

7a $R=OCH_3$; $R^1=H$; $R^4=COOCH_3$
8a $R=R^1=OCH_3$; $R^4=H$
8b $R=R^1=OCH_3$; $R^4=COOCH_3$

10a $R^2=OCH_3$; $R^3=H$
11a $R^2=R^3=OCH_3$

sulphate and anhyd. K_2CO_3 in acetone and the mixture of the corresponding methyl esters separated by preparative TLC to afford methyl 2-hydroxy-4,6-dimethoxybenzoate (**8b**) and methyl anisate (**10a**) from **5** and **8b** and methyl veratrate (**11b**) from **6**.

Similar results were obtained when this reaction was carried out in the presence of tetra-*n*-butylammonium hydrogen sulphate. However, in the absence of a quaternary ammonium salt, the resulting product was found to be a complex mixture.

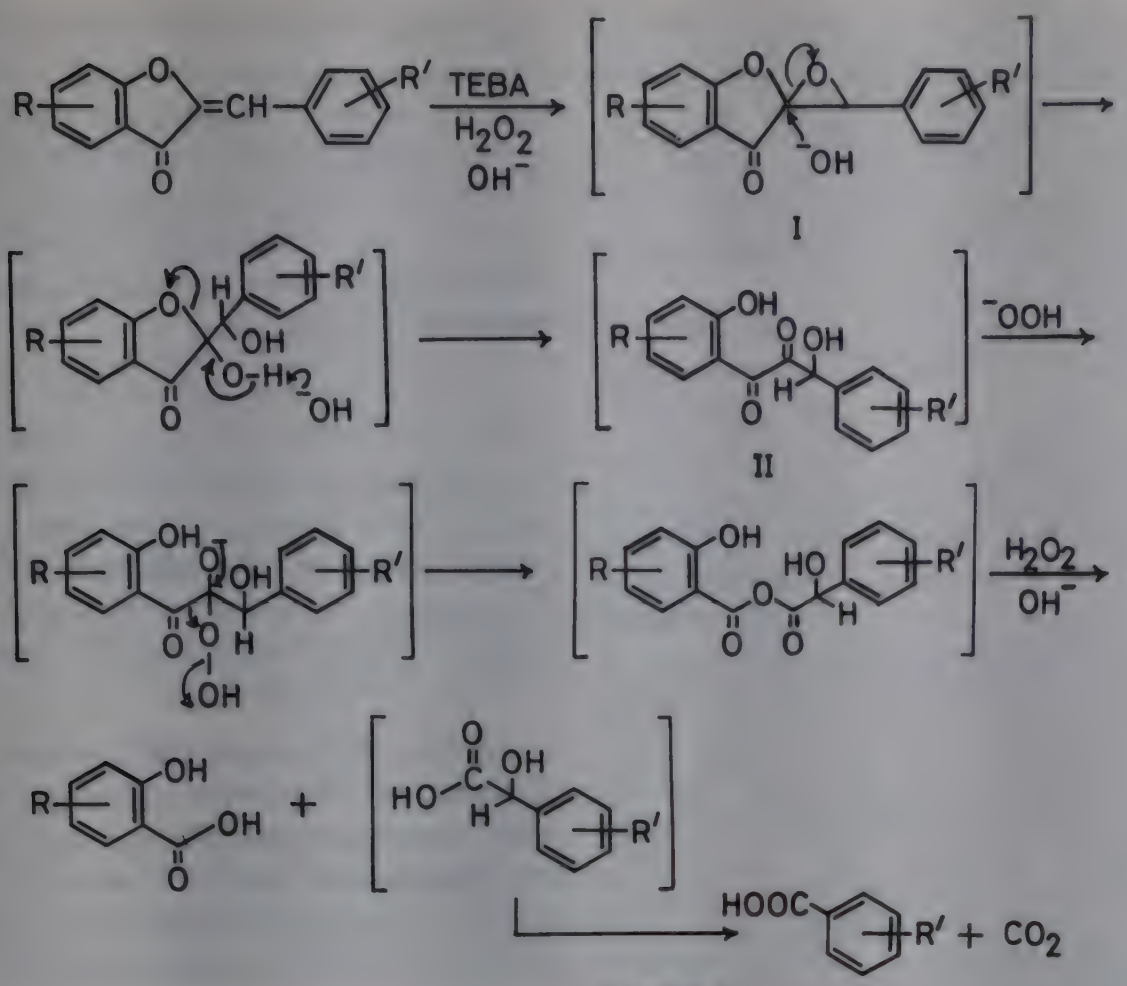
It appears quite plausible that the aurone epoxide (I), the formation of which is aided by the presence of a quaternary ammonium compound, undergoes ring opening to give the α-diketone (II) as shown in Scheme 1. The latter under the reaction conditions seems to undergo a ready cleavage to give a mixture of arylcarboxylic acid (from ring-A) and mandelic acid or its substituted derivative (from ring-B). The latter on further oxidation affords arylcarboxylic acid containing ring-B.

In support of this mechanism, it may be mentioned that benzils on treatment with alkaline hydrogen peroxide are reported to give arylcarboxylic acids derived from rings A and B[9]. Evidence for the last step in this mechanism was gathered by reacting mandelic acid with alkaline hydrogen peroxide in the presence of TEBA when benzoic acid was obtained in a quantitative yield.

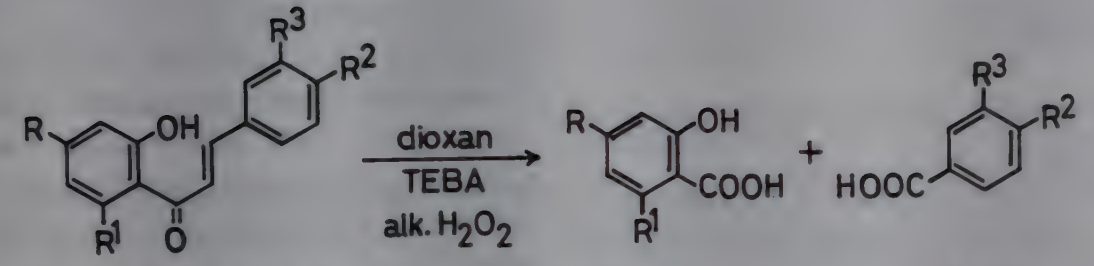
Identical results were obtained during attempted epoxidation of 2′-hydroxychalcones under the above conditions when these underwent facile cleavage to afford a mixture of arylcarboxylic acids derived from rings A and B. Separation of these acids was achieved by their preparative TLC or of their ester derivatives as mentioned above.

2′-Hydroxy-, 2′-hydroxy-4-methyoxy-, 2′-hydroxy-3,4-dimethoxy-, 2′-hydroxy-4′-methoxy-, 2′-hydroxy-4′-,4-dimethoxy-, 2′-hydroxy-4′,3,4-trimethoxy-, 2′-hydroxy-4′,6′-dimethoxy-, 2′-hydroxy-4′,6′,4-trimethoxy- and 2′-hydroxy-4′,6′,3,4-tetramethoxychalcones (**12-20**) underwent the above degradation on treatment with alkaline hydrogen peroxide thereby conforming the general applicability of the method.

The cleavage of 2′-hydroxychalcones appears to proceed through the intermediacy of the correspond-



Scheme 1



12,13,14,15,16,17,18,19,20

21,7,8

9,10,11

12 R=R^1=R^2=R^3=H

13 R=R^1=R^3=H; R^2=OCH_3

14 R=R^1=H; R^2=R^3=OCH_3

15 R=OCH_3; R^1=R^2=R^3=H

16 R=R^2=OCH_3; R^1=R^3=H

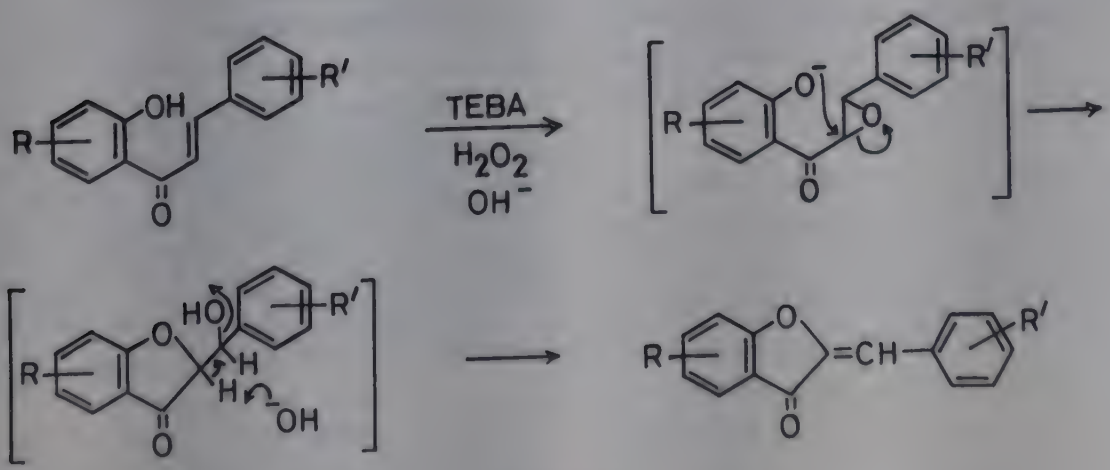
17 R=R^2=R^3=OCH_3; R^1=H

18 R=R^1=OCH_3; R^2=R^3=H

19 R=R^1=R^2=OCH_3; R^3=H

20 R=R^1=R^2=R^3=OCH_3

21 R=R^1=H



Scheme 2

ing aurones (Scheme 2), since these could be detected by TLC during initial stages of the reaction along with the products of cleavage and unreacted chalcones. However, attempts to isolate aurones during this cleavage proved unsuccessful, possibly because these underwent cleavage before an isolable quantity was formed in the reaction mixture.

It is of interest to note that earlier chemical degradation of aurones and chalcones for the purpose of determining their structures and substitution patterns in rings **A** and **B** was carried out under relatively drastic conditions (either boiling with conc. aq. alkali or fusion with alkali[10]) when fragments containing rings A and B were obtained in poor yields.

The present method, however, affords a mild diagnostic procedure for the structure elucidation of naturally occurring aurones and chalcones. This reaction was also carried out successfully using microquantities of aurones and chalcones and the products of cleavage were identified by co-TLC with authentic samples of arylcarboxylic acids, thus demonstrating its use as an analytical tool. This method, therefore, can be used as a complementary technique to support the structure arrieved at by spectroscopic methods[11].

Experimental Procedure

Cleavage of aurones with alkaline hydrogen peroxide in the presence of TEBA.

6-*Methoxyaurone* (**1**)—A mixture of **1**[12] (500 mg) in dioxan (6 ml), aq. sodium hydroxide (8%; 5 ml) and TEBA (500 mg) was magnetically stirred at room temperature and hydrogen peroxide (25%; 4 ml) added to it dropwise (during 15 min) while stirring. The reaction was monitored by TLC every 10 min, after acidification of a couple of drops of the reaction mixture and extraction with chloroform. Stirring was continued until the starting aurone **1** had completely reacted (1 hr). Ice was added to the reaction mixture and then extracted with chloroform. The aq. layer was acidified and the separated solid filtered and identified as 2-hydroxy-4-methoxybenzoic acid (**7**; 205 mg), m.p. 156-57° (lit.[13], m.p. 157°). Excess of sodium chloride was added to the filtrate when benzoic acid (**9**; 145 mg), m.p. and m.m.p. 121° was obtained.

6,4′-*Dimethoxyaurone* (**2**)[1]—A similar treatment of **2** (500 mg) in dioxan (6 ml) with aq. NaOH (8%; 5 ml), TEBA (500 mg) and H_2O_2 (25%; 4 ml) at room temperature for 40 min gave a solid (410 mg) which was found to be a mixture of two acids. This mixture, after drying in vacuum over P_2O_5 was refluxed with abs. methanol (15 ml) and conc. H_2SO_4 (2-3 drops) on a water-bath for 5 hr. Methanol was distilled off, and the residue treated with water and extracted with ether. The ether layer was washed with aq. sodium bicarbonate and then with water, dried, ether removed and the resudue subjected to preparative TLC (silica gel-G; benzene; double run). The two bands with R_f 0.75 and 0.59 were removed and eluted with acetone to give methyl 2-hydroxy-4-methoxybenzoate (**7a**; 200 mg) (m.p. 49°) and methyl anisate (**10a**; 185 mg) (m.p. 48°) respectively.

6,3′,4′-*Trimethoxyaurone* (**3**)[14]—Compound **3** (500 mg) in dioxan (6 ml) on a similar treatment at room temperature for 1 hr gave a solid (415 mg) which on preparative TLC (silica gel-G; 5% methanol-chloroform containing 2 drops of acetic acid) afforded 2-hydroxy-4-methoxybenzoic acid (**7**; 195 mg; R_f 0.44) (m.p. 157°) and veratric acid (**11**; 210 mg; R_f 0.52) (m.p. 180°; lit.[15], m.p. 181-82°).

4,6-*Dimethoxyaurone* (**4**)[16]—Aurone **4** (500 mg) in dioxan (6 ml) on a similar treatment for 50 min gave 2-hydroxy-4,6-dimethoxybenzoic acid (**8**; 200 mg) which was filtered, m.p. 154° (lit.[17], m.p. 152-54°). Saturation of the filtrate with sodium chloride afforded benzoic acid (**9**; 130 mg), m.p. and m.m.p. 121°.

4,6,4′-*Trimethoxyaurone* (**5**)[18]—Aurone **5** (500 mg) in dioxan (6 ml) on a similar treatment for 90 min gave an acid mixture (350 mg) which was refluxed with abs. methanol (15 ml) and conc. sulphuric acid (2-3 drops). It was worked up as above and the reaction product on preparative TLC (silica gel-G; benzene; single run) gave phloroglucinol dimethyl ether (**8a**; 150 mg, R_f 0.09) and methyl anisate (**10a**; 170 mg, R_f 0.41), m.p. 48°.

The reaction product (50 mg) was next methylated with dimethyl sulphate (0.03 ml) in acetone (5 ml) in the presence of anhyd. K_2CO_3 (0.5 g) in acetone (5 ml) and the methylated mixture separated by preparative TLC (silica gel-G; benzene-ethyl acetate; 3:1) to afford methyl 2-hydroxy-4,6-dimethoxybenzoate (**8b**, 18 mg; R_f 0.58; m.p. 107°; lit.[17], m.p. 107-9°) and methyl anisate (**10a**, 15 mg; R_f 0.68; m.p. 48°).

4,6,3′,4′-*Tetramethoxyaurone* (**6**)[19]—Aurone **6** (500 mg) in dioxan (6 ml) on a similar treatment for 2 hr gave an acid mixture (340 mg) which was treated with abs. methanol (15 ml) and conc. H_2SO_4 as above. Preparative TLC (silica gel-G; benzene; double run) of the methylated mixture afforded phloroglucinol dimethyl ether (**8a**; 140 mg; R_f 0.16) and methyl veratrate (**11a**; 170 mg; R_f 0.32; m.p. 58°).

The methylated mixture, obtained by dimethyl sulphate-acetone-K_2CO_3 method as described in the previous case, on preparative TLC (silica gel-G; benzene; single run) gave methyl 2-hydroxy-4,6-dimethoxybenzoate (**8b**; R_f 0.44; m.p. 107°) and methyl veratrate (R_f 0.32; m.p. 58°).

Cleavage of chalcones with alkaline hydrogen peroxide in the presence of TEBA.

2′-*Hydroxychalcone* (**12**)[4]—Chalcone **12** (200 mg) in dioxan (4 ml) was treated with aq. NaOH (8%; 4 ml), TEBA (200 mg) and H_2O_2 (25%; 3 ml) in a similar manner as aurone (*vide supra*). The reaction was monitored by TLC every 10 min as before. Among the new spots that were observed, two spots gave yellow colour with bromophenol blue. One of the two spots gave a positive ferric reaction and the other corresponded to the simple aurone[1] present in very small concentration. Stirring was continued until the starting chalcone (**12**) had disappeared (TLC; 3.5 hr). On working-up salicylic acid (**21**; 65 mg; m.p. 156°) separated out from the aq. layer on acidification. Saturation of the filtrate with sodium chloride afforded benzoic acid (**9**; 60 mg; m.p. 121°).

2′-*Hydroxy*-4-*methoxychalcones* (**13**)[4]—Chalcone **13** (200 mg) in dioxan (4 ml) on a similar treatment for 3 hr gave a solid (120 mg) which on preparative TLC (silica gel-G; 5% methanol-chloroform containing 2 drops of acetic acid) afforded salicylic acid (**21**; 55 mg; R_f 0.65; m.p. 156°) and anisic acid (**10**; 60 mg; R_f 0.80; m.p. 182-83°).

2′-*Hydroxy*-3,4-*dimethoxychalcone* (**14**)[4]—Chalcone **14** (200 mg) on a similar treatment for 2 hr afforded salicylic acid (**21**; 55 mg; R_f 0.65; m.p. 156°) and veratric acid (**11**; 70 mg; R_f 0.52; m.p. 180°) which were separated as in the previous case.

2′-*Hydroxy*-4′-*methoxychalcone* (**15**)[4]—Chalcone **15** (200 mg) in dioxan (4 ml) on a similar treatment for 1.5 hr afforded 2-hydroxy-4-methoxybenzoic acid (**7**; 70 mg; m.p. 157°) and benzoic acid (**9**; 50 mg; m.p. 121°).

2′-*Hydroxy*-4′,4-*dimethoxychalcone* (**16**)[4]—Chalcone **16** (200 mg) in dioxan (4 ml) on a similar treatment for 1 hr gave an acid mixture (140 mg) which was refluxed with abs. methanol (10 ml) and conc. H_2SO_4 (2-3 drops) on a water-bath for 5 hr. The reaction product on preparative TLC (silica gel-G; benzene; double run) gave methyl 2-hydroxy-4-methoxybenzoate (**7a**; 65 mg; R_f 0.75; m.p. 49°) and methyl anisate (**10a**; 60 mg; R_f 0.59; m.p. 48°).

2′-*Hydroxy*-4′,3,4-*trimethoxychalcone* (**17**)[4]—A similar treatment of **17** (200 mg) for 1.5 hr afforded an acid mixture (150 mg) which on preparative TLC (silica gel-G; 5% methanol-chloroform containing 2 drops of acetic acid) afforded 2-hydroxy-4-methoxybenzoic acid (**7**; 65 mg; R_f 0.44; m.p. 157°) and veratric acid (**11**; 70 mg; R_f 0.52; m.p. 180°).

2′-*Hydroxy*-4′,6′-*dimethoxychalcone* (**18**)[4]—Chalcone **18** (200 mg) in dioxan (4 ml) on a similar treatment for 80 min gave 2-hydroxy-4,6-dimethoxybenzoic acid (**8**; 80 mg; m.p. 154°) and benzoic acid (**9**; 60 mg; m.p. 121°).

2′-*Hydroxy*-4′,6′,4-*trimethoxychalcone* (**19**)[4]—Chalcone **19** (200 mg) on a similar treatment for 2 hr afforded an acid mixture (110 mg) which was refluxed with abs. methanol and conc. H_2SO_4 and the methylated product subjected to preparative TLC to give phloroglucinol dimethyl ether (**8a**; 40 mg; R_f 0.09, silica gel-G, benzene, single run) and methyl anisate (**10a**; 45 mg; R_f 0.41).

The acid mixture on refluxing with dimethyl sulphate in acetone containing anhyd. K_2CO_3 followed by preparative TLC gave methyl 2-hydroxy-4,6-dimethoxy-benzoate (m.p. 107°) and methyl anisate (m.p. 48°).

2′-*Hydroxy*-4′,6′,3,4-*tetramethoxychalcone* (**20**)[4]—Chalcone **20** (200 mg) in dioxan (4 ml) on a similar treatment for 2.5 hr gave a solid (125 mg) which was refluxed with abs. methanol and conc. H_2SO_4 and the product subjected to preparative TLC (silica gel-G; benzene; double run) to afford phloroglucinol dimethyl ether (**8a**; 45 mg; R_f 0.16) and methyl veratrate (**11a**, 60 mg; R_f 0.32).

The acid mixture on refluxing with dimethyl sulphate in acetone containing anhyd. K_2CO_3 followed by preparative TLC gave methyl 2-hydroxy-4,6-dimethoxybenzoate (m.p. 107°) and methyl veratrate (m.p. 58°).

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Aromatic Benzhydrylation: Part VII—Synthesis of Benzhydrylated 2,4,6-Trihydroxypropiophenones & 5,7-Dihydroxy-2,3-dimethylchromones

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2,4,6-Trihydroxypropiophenone (**1**) reacts with diphenylcarbinol in the presence of $BF_3.Et_2O$ to give 3,5-bis-diphenylmethyl (**2a**) and 3-diphenylmethyl (**3a**) derivatives which on heating with acetic anhydride and sodium acetate followed by hydrolysis afford the corresponding 5,7-dihydroxychromones (**4b** and **5b** respectively). In order to locate the position of diphenylmethyl group in **5b**, 2,3-dimethyl-5,7-dihydroxychromone (**6**) has directly been benzhydrylated to give a mixture of **4b**, **5b** and its isomer **7b**. Comparison of the chemical shifts for **5b** and **7b** and their acetates leads to the assigned structures.

In continuation of our work on the synthesis of benzhydrylated polyphenols as analogues of naturally occurring and biologically active melanervin[1-6], we have carried out benzhydrylation of 2,4,6-trihydroxy-propiophenone[7] (**1**) with diphenylcarbinol in the presence of $BF_3.Et_2O$. The product was a mixture of two compounds separable by column chromatography. The first product was identified as 3,5-bisdiphenylmethyl-2,4,6-trihydroxypropiophenone (**2a**) on the basis of formation of a trimethyl ether (**2b**) [PMR: δ2.60 (*s*, 3H, OCH_3) and 2.85 (*s*, 6H, 2 $\times OCH_3$)]. Further, the PMR spectra of **2a** and **2b** showed no aromatic proton of the starting material but exhibited signals due to two diphenylmethyl groups (see Experimental). The second product was similarly identified as 3-diphenylmethyl-2,4,6-trihydroxy-propiophenone (**3a**) which formed a trimethyl ether (**3b**).

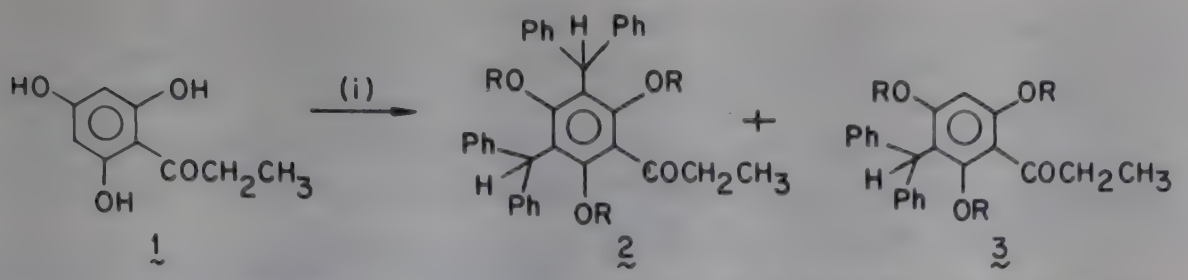
The benzhydrylated propiophenones **2a** and **3a** on Perkin reaction with acetic anhydride and fused sodium acetate gave the corresponding 2,3-dimethyl-5,7-diacetoxychromones (**4a** and **5a**) in good yields. Hydrolysis of these acetoxychromones gave the corresponding hydroxychromones (**4b** and **5b**). The former (**4b**) was easily identified on the basis of its UV and PMR spectra. However, the latter could be either 6-C- or 8-C-diphenylmethyl isomer. Its location in 6-position was made by preparing the alternative isomer and then comparing the chemical shifts for aromatic protons. This was accomplished by direct benzhydrylation of 2,3-dimethyl-5,7-dihydroxy-chromone[8] (**6**) when a mixture of three products was obtained. Two of the products were identical with **4b** and **5b**; the third product was found isomeric to **5b** on the basis of its elemental analysis and PMR spectrum. Hence, it should be the alternative diphenylmethyl isomer **7b**. In confirmation of the assigned structures (**5b** and **7b**), the triphenylmethine proton was more deshielded in **7b** than in **5b**. Similarly, the aromatic proton of the condensed benzene ring was more deshielded in **7a** and **7b** than in **5a** and **5b** respectively. The hydroxychromone (**4b**) was also converted into its methyl ethers (**4c** and **4d**).

Experimental Procedure

Unless stated otherwise, all m.ps are uncorrected; petrol used had the boiling range 60-80°; silica gel was used for column chromatography and TLC; solvent systems used for TLC were: (A) benzene, (B) benzene-ethyl acetate (19:1); R_f refers to TLC; UV spectra were recorded in MeOH on a Perkin-Elmer 554 spectrophotometer (λ_{max} in nm and log ε in parenthesis); IR spectra in KBr were run on a Shimadzu model 535 spectrophotometer (ν_{max} in cm^{-1}); PMR spectra were taken in $CDCl_3$ on a Perkin-Elmer 90 MHz model R-32 instrument using TMS as internal standard (chemical shifts in δ ppm and J values in Hz).

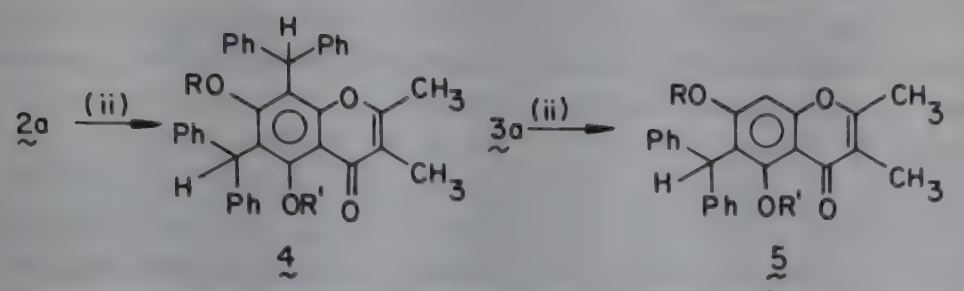
Reaction of 2,4,6-*trihydroxypropiophenone* (**1**) with *diphenylcarbinol*

To a stirred solution of **1**[7] (4.66 g, 25.6 mmol) in dry dioxan (80 ml) was added a solution of diphenylcarbinol (4.71 g, 25.6 mmol) in dioxan (20 ml) followed by addition of $BF_3.Et_2O$ (40 ml) in small lots. The resulting mixture was stirred and heated at 60-70° for 4 hr, cooled, diluted with ether (400 ml). The ethereal layer was washed with water, dried, solvent evaporated to dryness and the residue subjected to column chromatography. Successive elution of the column



1 2 3

For 2 & 3: a, R = H; b, R = CH_3



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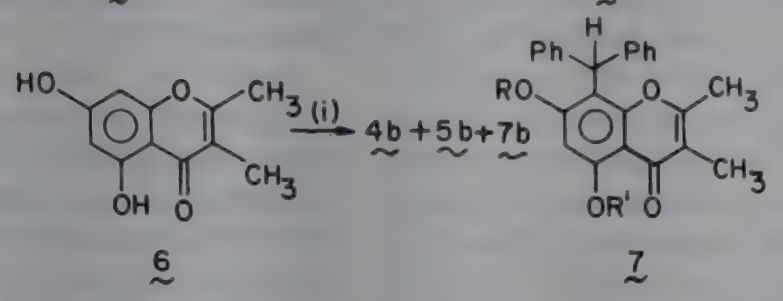

6 7

For 4, 5, & 7: (a) R = R' = $COCH_3$; (b) R = R' = H
(c) R = CH_3, R' = H ; (d) R = R' = CH_3

Reagents used: (i) Ph_2CHOH, BF_3—Et_2O,  ; (ii) Ac_2O–NaOAc, 180°

with (i) petrol-benzene (9:1), (ii) petrol-benzene (1:1) and (iii) benzene afforded three fractions A-C.

Fraction A—It crystallised from petrol-benzene to give 3,5-bisdiphenylmethyl-2,4,6-trihydroxypropiophenone (**2a**) as light yellow crystals (1.4 g), m.p. 249-50°; R_f 0.72 (solvent B) (Found: C, 81.5; H, 5.8. $C_{35}H_{30}O_4$ requires C, 81.7; H, 5.9%); UV: 220 (4.42), 286 (4.78) and 296 (4.75); IR: 3400, 1640, 1420, 1215, 1140 and 825; PMR: 1.05 (*t*, *J* = 7, 3H, CH_3CH_2—), 2.90 (*q*, *J* = 7, 2H, CH_3-CH_2), 6.11 [*s*, 2H, 2 × $CH(Ph)_2$], 7.22 (*bm*, 20H, 4 × C_6H_5), and 10.14 (*s*, 1H, chelated OH).

It formed a trimethyl ether (**2b**) by treatment with Me_2SO_4-K_2CO_3 in acetone (10 hr) which crystallised from petrol-benzene as white needles, m.p. 198-99°; R_f 0.64 (solvent A) (Found: C, 82.1; H, 6.4. $C_{38}H_{36}O_4$ requires C, 82.0; H, 6.5%); UV: 261, 286 and 296; PMR: 1.08 (*t*, *J* = 7, 3H, CH_3CH_2-), 2.60 and 2.91 (2*s*, 9H, 3 × OCH_3), 2.80 (*q*, *J* = 7, 2H, $-CH_2CH_3$), 6.01 [*s*, 2H, 2 × $CH(Ph)_2$], and 7.20 (*bm*, 20H, 4 × C_6H_5).

Fraction B—It crystallised from petrol-benzene to give 3-diphenylmethyl-2,4,6-trihydroxypropiophenone (**3a**) as light yellow plates (2.5 g), m.p. 155-56°; R_f 0.54 (solvent B) (Found: C, 75.9; H, 5.7. $C_{22}H_{20}O_4$ requires C, 75.8; H, 5.8%); UV: 258 (4.59) and 281 (4.48); IR: 3400, 1620, 1422, 1220, 1075 and 818; PMR: 1.14 (*t*, *J* = 7, 3H, CH_3-CH_2), 3.02 (*q*, *J* = 7, 2H, $-CH_2CH_3$), 5.78 [*s*, 1H, $CH(Ph)_2$], 6.06 (*s*, 1H, C_5-H), 7.19 (*bm*, 10H, 2 × C_6H_5), 12.60 (*s*, 1H, chelated OH).

It formed a trimethyl ether (**3b**) (Me_2SO_4-K_2CO_3-acetone, 4 hr) which crystallised from methanol as colourless plates, m.p. 156-57°; R_f 0.56 (solvent A) (Found: C, 76.5; H, 6.6. $C_{25}H_{26}O_4$ requires C, 76.9; H, 6.7%); UV: 258 (4.59), 281 (4.48) and 296 (4.64); PMR: 1.22 (*t*, *J* = 7, 3H, CH_3-CH_2—), 2.82 (*q*, *J* = 7, 2H, $-CH_2CH_3$), 3.30, 3.53 and 3.80 (3*s*, 3H each, 3 × OCH_3), 5.92 [*s*, 1H, $CH(Ph)_2$], 6.24 (*s*, 1H, C_5-H), and 7.18 (*bm*, 10H, 2 × C_6H_5).

Fraction C—It crystallised from ethanol to give the starting material (0.4 g) m.p. and m.m.p. 174-75° (lit.[7], m.p. 174-75°).

5,7-Diacetoxy-6,8-bisdiphenylmethyl-2,3-dimethylchromone (**4a**) *and its derivatives* (**4b**, **4c** *and* **4d**)

A mixture of **2a** (500 mg), fused sodium acetate (600 mg) and freshly distilled acetic anhydride (10 ml) was refluxed in an oil-bath initially for 1 hr at 140-45° and then at 180-90° for 6 hr. The mixture was cooled and poured over crushed ice and the solid collected and

crystallized from methanol to give **4a** as light brown crystals, m.p. 202°; R_f 0.57 (solvent A) (Found: C, 79.0; H, 5.6. $C_{41}H_{34}O_6$ requires C, 79.1; H, 5.5%); UV: 240 (5.03), 306 (4.35) and 333 (4.50); PMR: 1.86 (*s*, 6H, 2 × CH_3), 1.82, 1.88 (*s*, 6H, 2 × $OCOCH_3$), 5.61 and 5.70 [2*s*, 1H each, 2 × $-CH(Ph)_2$], and 7.09 (*bm*, 20H, 4 × C_6H_5).

The above chromone (200 mg) on refluxing with 10% aq. Na_2CO_3 gave 6,8-bisdiphenylmethyl-5,7-dihydroxy-2,3-dimethylchromone (**4b**) (150 mg) which crystallised from methanol as light yellow needles, m.p. 243-44°; R_f 0.64 (solvent B) (Found: C, 82.4; H, 5.7. $C_{37}H_{30}O_4$ requires C, 82.5; H, 5.6%); UV: 266 (4.42) and 304 (4.42); IR: 3300, 1640, 1580, 1430, 1250 and 1025; PMR: 1.79 and 1.92 (2*s*, 3H each, 2 × $-CH_3$), 5.92 and 6.11 [2*s*, 1H each, 2 × $CH(Ph)_2$], 7.06 (*bm*, 20H, 4 × C_6H_5-), and 13.88 (*s*, 1H, chelated OH).

7-Methyl ether (**4c**) was prepared by treating **4b** with Me_2SO_4 (1 mol equiv) in acetone containing K_2CO_3 for 0.5 hr and crystallised from methanol as white needles, m.p. 223-24°; R_f 0.54 (solvent A) (Found: C, 82.5; H, 5.7. $C_{38}H_{32}O_4$ requires C, 82.6; H, 5.8%); UV: 264 (4.72), 298 (4.24) and 299 (4.34); PMR: 1.80 and 1.89 (2*s*, 3H each, 2 × CH_3), 3.03 (*s*, 3H, $-OCH_3$), 5.94 and 5.98 [2*s*, 1H each, 2 × $CH(Ph)_2$], 7.11 (*bm*, 20H, 4 × C_6H_5), and 13.52 (*s*, 1H, chelated OH).

5,7-Dimethyl ether (**4d**) was obtained by treating **4b** with Me_2SO_4 (2.5 mol equiv) in acetone containing K_2CO_3 for 12 hr and crystallised from benzene-petrol as white needles, m.p. 203-4°; R_f 0.59 (solvent A) (Found: C, 82.4; H, 5.8. $C_{39}H_{34}O_4$ requires C, 82.7; H, 6.1%); UV: 264, 300 and 315; IR: 1625, 1430, 1240 and 1040; PMR: 1.88 and 1.90 (*s*, 6H, 2 × CH_3-), 2.97 and 3.11 (2*s*, 3H each, 2 × $-OCH_3$), 6.11 and 6.18 [2*s*, 1H each, 2 × $CH(Ph)_2$], and 7.18 (*bm*, 20H, 4 × C_6H_5).

5,7-Diacetoxy-6-diphenylmethyl-2,3-dimethylchromone (**5a**) *and its hydrolysis product* (**5b**)

Treatment of **3a** (500 mg) with fused sodium acetate (600 mg) and acetic anhydride (15 ml) followed by work-up as in the case of **2a**, gave **5a** which crystallized from ethanol as light brown crystals (600 mg), m.p. 124°; R_f 0.42 (solvent A) (Found: C, 73.4; H, 5.5. $C_{28}H_{24}O_6$ requires C, 73.7; H, 5.3%); UV: 264 (4.58) and 303 (4.63); PMR: 1.66 and 1.76 (2*s*, 3H each, 2 × $-CH_3$), 2.03 and 2.25 (2*s*, 3H each, 2 × $OCOCH_3$), 5.87 [*s*, 1H, $CH(Ph)_2$], 6.58 (*s*, 1H, C_8-H) and 7.05 (*bm*, 10H, 2 × C_6H_5).

The above chromone on refluxing with 10% Na_2CO_3 (20 ml) for 2 hr gave 6-diphenylmethyl-5,7-dihydroxy-2,3-dimethylchromone (**5b**) which crystallised from methanol as light yellow plates (150 mg), m.p. 164°; R_f 0.37 (solvent B) (Found: C, 77.2; H, 5.5; $C_{24}H_{20}O_4$ requires C, 77.4; H, 5.4%); UV: 262 (4.7), 299 (4.33) and 324 (4.23); IR: 3300, 1642, 1415, 1230, 1070 and 690; PMR: 1.93 and 2.15 (2*s*, 3H each, 2 × CH_3-), 6.00 [*s*, 1H, $CH(Ph)_2$], 6.16 (*s*, 1H, C_8-H), 7.14 (*bm*, 10H, 2 × C_6H_5), and 13.26 (*s*, 1H, chelated OH).

Reaction of 5,7-dihydroxy-2,3-dimethylchromone (**6**) *with diphenylcarbinol*

To a stirred solution of **6**[8] (4.04 g, 19.2 mmol) in dry dioxan (90 ml) was added a solution of diphenylcarbinol (3.6 g, 19.2 mmol) in dioxan (10 ml) followed by $BF_3.Et_2O$ (30 ml) in small lots. The product on column chromatography and successive elution with (i) petrol-benzene (19:1), (ii) petrol-benzene (9:1) (iii) petrol-benzene (2:1) and (iv) benzene gave the following four fractions (D-G).

Fraction D—It gave **4b** (0.7 g).

Fraction E—It crystallised from benzene to give 8-diphenylmethyl-5,7-dihydroxy-2,3-dimethylchromone (**7b**) as cream coloured crystals (1.1 g), m.p. 170°; R_f 0.40 (solvent B) (Found: C, 77.2; H, 5.5. $C_{24}H_{20}O_4$ requires C, 77.4; H, 5.4%); UV: 266 (4.57), 297 (4.38) and 312 (4.18); IR: 3200, 1620, 1410, 1340, and 1180; PMR: 2.13 and 2.60 (2*s*, 3H each, 2 × $-CH_3$), 6.21 [*s*, 1H, $CH(Ph)_2$], 6.72 (*s*, 1H, C_6-H), 7.33 (br *m*, 10H, 2 × C_6H_5), and 13.3 (*s*, 1H, chelated OH).

The diacetate, prepared by keeping **7b** with acetic anhydride and pyridine at room temperature overnight, was crystallised from chloroform as light brown crystals (0.5 g), m.p. 130-31°; R_f 0.44 (solvent A) (Found: C, 72.1; H, 5.4. $C_{26}H_{24}O_6$ requires C, 72.2; H, 5.6%); UV: 266 (4.58) and 304 (4.64); 200 MHz PMR: 1.80 and 2.00 (2*s*, 3H each, 2 × CH_3-), 2.24 and 2.36 (2*s*, 3H each, 2 × $OCOCH_3$), 5.88 [*s*, 1H, $CH(Ph)_2$], 7.16 (*s*, 1H, C_6-H), and 7.21 (*m*, 10H, 2 × C_6H_5).

Fraction F—It afforded **5b** (0.5 g).

Fraction G—It crystallised from ethanol to give the starting material (0.4 g).

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Synthesis of 5-Deoxykievitone Dimethyl Ether & Related Isopentenylated Isoflavanones

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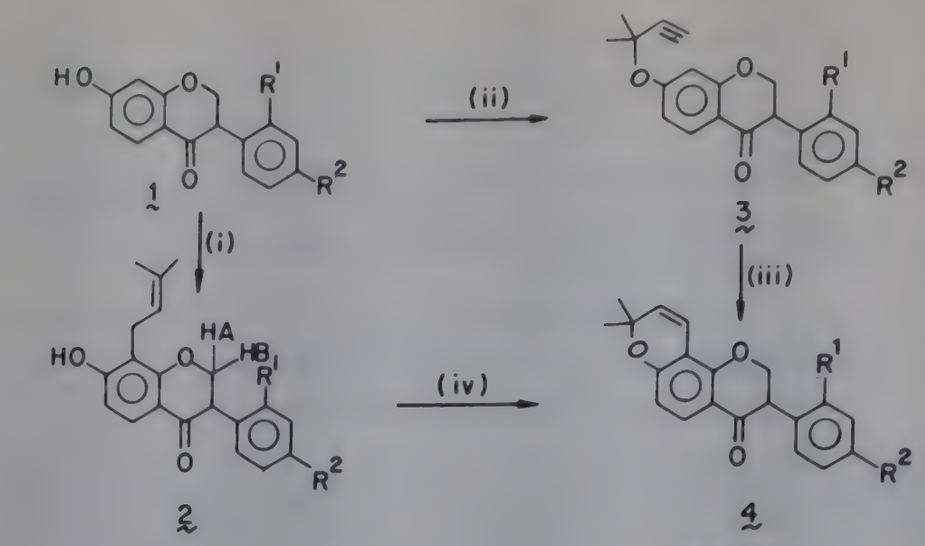
Three different 7-hydroxyisoflavanones (**1a**, **1b** and **1c**) have been converted into the corresponding 6″,6″-dimethylpyrano[2″,3″:7,8]isoflavanones (**4a**, **4b** and **4c**) either through their 8-(3,3-dimethylallyl) derivatives (**2a**, **2b** and **2c**) or their 1,1-dimethylpropargyl ethers (**3a**, **3b** and **3c**). Among them, **2c** is the dimethyl ether of naturally occurring 5-deoxykievitone. Attempts to synthesize the natural product itself by this route have been unsuccessful because demethylation of the starting desoxybenzoin (**5**) gives the corresponding 2-arylbenzofuran derivative (**7a**).

As many as seventeen isopentenylated isoflavanones are known to occur in nature[1]. However, none of them has been synthesised so far. This was mainly due to lack of availability of a good synthetic method for preparing hydroxyisoflavanones. Since such a general method has been devised now in this laboratory[2,3], synthesis of isopentenylated isoflavanones has been undertaken. Before attempting the synthesis of the simplest compound, viz. 5-deoxykievitone (7,2′,4′-trihydroxy-8-*C*-prenylisoflavanone, **2d**) isolated from *Phaseolus vulgaris* by Woodward *et al.*[4], the known methods of isopentenylation were studied on 7-hydroxyisoflavanone[3] (**1a**) and 7-hydroxy-4′-methoxyisoflavanone[3] (**1b**) as model experiments to standardise conditions.

7-hydroxyisoflavanone (**1a**) when reacted with 3-methylbut-1-en-3-ol in dioxan and boron trifluoride etherate resulted in a mixture of products out of which only 7-hydroxy-8-C-prenylisoflavanone (**2a**) could be isolated chromatographically. This was characterized by its PMR spectrum which showed only two *ortho* coupled doublets at δ 6.40 and 7.70 and the presence of one C-prenyl unit (signals due to one *gem*-dimethyl group at δ 1.62 and 1.70, a doublet for benzylic group at 3.78 and an olefinic proton at 4.74). Its cyclodehydrogenation with DDQ afforded 6″,6″-dimethylpyrano[2″,3″:7,8]isoflavanone (**4a**) which could also be synthesised by an alternate route from the same isoflavanone (**1a**) as follows. 1,1-Dimethylpropagylation of **1a** with 3-chloro-3-methyl-1-butyne in the presence of dry potassium carbonate and potassium iodide in acetone furnished 7-propargyloxyisoflavanone (**3a**) as shown by its IR, PMR and ^{13}C-NMR spectra. The PMR spectrum of **3a** showed an acetylenic proton at δ 2.60 and a *gem*-dimethyl group at 1.28 besides signals of the parent compound. IR absorptions appeared at 2220 and 3290 cm^{-1} due to $-C\equiv C-H$ function and the off-resonance ^{13}C-NMR spectrum exhibited a doublet at δ 101.50 and a singlet at 84.5 due to acetylenic carbons, a doublet at 52.11 due to C-3 and a triplet at 71.87 due to C-2 indicating the isoflavanone skeleton to be intact. The second stage involved thermal cyclisation of **3a** in the presence of N,N-dimethylaniline. The resultant pyranoisoflavanone (**4a**) was characterized by its PMR and ^{13}C-NMR spectra. The PMR spectrum showed two doublets at δ 5.50 and 6.50 having $J = 9.5$ Hz due to vicinal olefinic protons and a singlet due to *gem*-dimethyl protons at 1.42; the off-resonance ^{13}C-NMR spectrum showed a doublet at δ 51.99 due to C-3, a triplet at 72.66 due to C-2 and two doublets at 115.72 and 127.04 due to olefinic carbons.

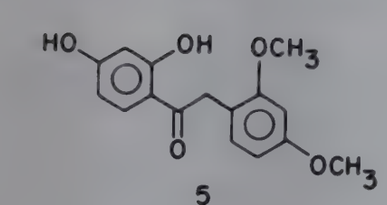
A parallel series of experiments with 7-hydroxy-4′-methoxyisoflavanone[3] (**1b**) and 7-hydroxy-2′,4′-dimethoxyisoflavanone[7] (sativanone; **1c**) gave the corresponding pyranoisoflavanones (**4b** and **4c** respectively) through their propargyl ethers (**3b** and **3c**). Further, the nuclear prenylation of sativanone (**1c**) with 3-methyl-but-1-en-3-ol in the presence of BF_3-Et_2O and dioxan gave 8-C-prenyl derivative (**2c**) which is the dimethyl ether of naturally occurring compound (±)-5-deoxykievitone.

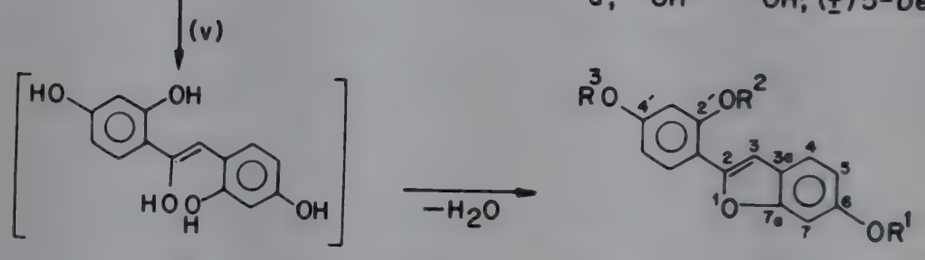
For the synthesis of (±)-5-deoxykievitone itself, demethylation of 2,4-dihydroxy-2′,4′-dimethoxy-desoxybenzoin (**5**) with pyridinium bromide was attempted. However, the product was not the demethylated one but a cyclisation product which was identified as 6-hydroxy-2-(2′,4′-dihydroxy-phenyl)benzofuran (**7a**) on the basis of its elemental analysis, PMR and ^{13}C-NMR spectra. It gave a light-green ferric reaction. Its IR spectrum showed only the presence of phenolic group (ν_{max} 3300 cm^{-1}) and no carbonyl function; PMR spectrum showed all the aromatic protons of the starting compound, but there was a singlet for an olefinic proton at δ 6.94; the off-resonance ^{13}C-NMR spectrum showed olefinic carbon



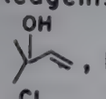
For 1–4

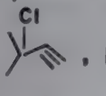
	R^1	R^2
a,	H	H
b,	H	OCH_3
c,	OCH_3	OCH_3
d,	OH	OH; (±)5-Deoxykievitone





Reagents used:

(i)  , BF_3-Et_2O, dioxan

(ii)  , K_2CO_3, Me_2CO, KI, Δ

(iii) $PhNMe_2$, Δ

(iv) DDQ, C_6H_6

(v) $[PyrH]^+ Br^-$, Δ

	R^1	R^2	R^3
a,	H	H	H
b,	CH_3	CH_3	CH_3
c,	Ac	Ac	Ac

as a doublet at δ 99.08 besides other signals. Further, it formed a trimethyl ether (**7b**) (signals for OCH_3 groups at δ 3.75 and 3.86) and triacetate **7c** (signals for $OCOCH_3$ groups at δ 2.25, 2.27 and 2.35). Thus, a method for preparing 5-deoxykievitone has to be designed.

Experimental Procedure

Unless stated otherwise, all m.ps are uncorrected; pet. ether had a boiling range 60-80°; silica gel was used for column chromatography and TLC; solvent systems for TLC were (A) benzene, (B) benzene-ethyl acetate (19:1) and (C) benzene-ethyl acetate (7:3); R_f values refer to TLC; UV data were recorded in methanol on a Perkin-Elmer model-554 spectrophotometer (λ_{max} in nm and log ε in parentheses); IR spectra were recorded in KBr on a Shimadzu IR-435 spectrophotometer (ν_{max} in cm^{-1}); some PMR spectra were recorded on a 90 MHz R-32 Perkin-Elmer spectrometer and the rest of PMR spectra and ^{13}C-NMR spectra on a Jeol FX-200 (200 MHz) instrument in $CDCl_3$ using MTMS as an internal standard (chemical shifts in δ, ppm).

Prenylation of Isoflavanone (**1a**) *and* (**1c**): *Formation of 8-C-prenyl derivatives* (**2a** *and* **2c** *respectively*)

A solution of the isoflavanone (1 mmol) in dry dioxan (15 ml) was stirred at room temperature with BF_3-Et_2O (0.2 ml) and 3-methyl-but-1-en-3-ol (0.2 ml) for 8 hr, diluted with ether (100 ml) and the ether layer washed with H_2O twice, dried and the residue purified by column chromatography to give **2a** or **2c**.

7-Hydroxy-8-C-prenylisoflavanone (**2a**):

Oil (12 mg), R_f 0.48 (solvent-A); UV: 285 and 317; IR: 3400, 1640, 1608 and 1600; 90 MHz PMR: 1.62 and 1.70 [2*s*, 3H each, $(CH_3)_2C=$], 3.78 (*t*, $J=8.0$ Hz, 3H, C_3-H and $=CH-CH_2Ar$), 4.60 (*d*, $J=6.0$ Hz, 2H, C_2-H_2), 4.74 (*d*, $J=8.0$ Hz, 1H, $CH_2-CH=$), 6.40 (*d*, $J=9.5$ Hz, 1H, C_6-H), 7.30 (*m*, 5H, C_6H_5), and 7.70 (*d*, $J=9.5$ Hz, 1H, C_5-H).

7-Hydroxy-2′,4′-dimethoxy-8-C-prenylisoflavanone or 5-deoxykievitone dimethyl ether (**2c**):

Colourless oil, R_f 0.60 (solvent-C); UV: 268 and 312; IR: 1640, 1605, 1590 and 1580; 200 MHz PMR: 1.66, 1.78 [2*s*, 3H each, $(CH_3)_2C=$] 3.55 (*d*, $J=8.0$ Hz, 2H, CH_2Ar), 3.80 (*s*, 6H, $2\times-OCH_3$), 3.84 (*dd*, $J=9.2$ Hz and 6.0 Hz, 1H, C_3-H), 4.43 (*dd*, $J=11.8$ and 9.2 Hz, 1H, C_2-H_B), 4.56 (*dd*, $J=11.80$ and 6.0 Hz, 1H, C_2-H_A), 5.10 (*m*, 1H, $CH_2=CH$), 6.40-6.60 (*m*, 3H, $C_{3'}$-H, $C_{5'}$-H and C_6-H), 7.23 (*d*, $J=9.5$ Hz, 1H, $C_{6'}$-H) and 7.80 (*d*, $J=9.5$ Hz, 1H, C_5-H).

1,1-Dimethylpropargylation of 7-hydroxyisoflavanone (**1a**, **1b** *and* **1c**)

A solution of the hydroxyisoflavanone (1 mmol) in acetone (10 ml) was refluxed with 3-chloro-3-methyl-1-butyne[5] with anhyd. K_2CO_3 (720 mg) and KI (350 mg) for 70 hr. The solvent was removed and water (100 ml) added to the residue. The product was purified by column chromatography to give **3a-c**.

7-(1,1-Dimethylpropargyloxy)isoflavanone (**3a**)

Colourless oil, R_f 0.53 (solvent-A); UV: 260 and 310; IR: 3290, 2220, 1665 and 1600; 90 MHz PMR: 1.28 [*s*, 6H, $(CH_3)_2C<$], 2.60 (*s*, 1H, $C=C-H$), 3.85 (*d*, 1H, C_3-H), 4.55 (*d*, $J=6.0$ Hz, 2H, C_2-H_2), 6.70 (*dd*, $J=9.5$ and 2.5 Hz, 2H, C_6-H and C_8-H), 7.20 (*m*, 5H, $1\times C_6H_5$-), and 7.76 (*d*, $J=9.5$ Hz, 1H, C_5-H); 50 MHz ^{13}C-NMR: 29.73 (*m*, $2\times-CH_3$), 52.11 (*d*, C-3), 71.87 (*t*, C-2), 75.10 (*s*, C-6″), 84.50 (*s*, $-C\equiv CH$), 101.50 (*d*, $-C\equiv C-H$), 106.29 (*d*, C-8), 114.02 (*d*, C-6), 115.60 (*s*, C-4a), 127.64 (*d*, C-4′), 128.29 (*d*, C-2′ and C-6′), 128.79 (*d*, C-5, C-3′ and C-5′), 134.80 (*s*, C-1′), 162.54 (*s*, C-8a), 163.54 (*s*, C-7), and 190.94 (*s*, CO).

4′-Methoxy-7-(1,1-dimethylpropargyloxy)isoflavanone (**3b**)

Colourless oil, R_f 0.73 (solvent-A); UV: 274 and 314; IR: 2240, 1630, 1600 and 1580; 200 MHz PMR (acetone-d_6): 1.72 [*s*, 6H, $(CH_3)_2C<$], 2.64 (*s*, 1H, $-C\equiv C-H$), 3.78 (*s*, 3H, OCH_3), 4.14 (*t*, 1H, C_3-H), 4.60 (*d*, $J=6.0$ Hz, 2H, C_2-H_2), 6.88 (*m*, 4H, C_6-H, C_8-H, $C_{3'}$-H and $C_{5'}$-H), 7.27 (*d*, $J=9.5$ Hz, 2H, $C_{2'}$-H and $C_{6'}$-H) and 7.86 (*d*, $J=9.5$ Hz, IH, C_5-H).

2′,4′-Dimethoxy-7-(1,1-dimethylpropargyloxy)-isoflavanone (**3c**)

Yellow oil, R_f 0.58 (solvent-B); UV: 273 and 313; IR: 3290, 2210, 1665 and 1605; 90 MHz PMR: 1.50, 1.57 [2*s*, 3H each, $(CH_3)_2C<$], 2.47 (*s*, 1H, $-C\equiv C-H$), 3.60 (*s*, 6H, $2\times OCH_3$), 4.33 (*dd*, 1H, C_3-H), 4.65 (*dd*, 2H, C_2-H_2), 6.40 (*m*, 4H, $C_{3'}$H, $C_{5'}$H, C_6-H and C_8-H), 6.93 (*d*, $J=9.5$ Hz, 1H, $C_{6'}$H), and 7.87 (*d*, $J=9.5$ Hz, 1H, C_5-H).

6″,6″-Dimethylpyrano[2″,3″:7,8]isoflavanones (**4a**, **4b** *and* **4c**): *First method*

A solution of 8-C-prenylisoflavanone (**2a**, 1 mmol) in dry benzene (12 ml) was treated with DDQ[6] (70 mg) and the solution heated on a boiling water-bath for 25 min when the colourless hydroquinone separated out. It was filtered while hot and the residue washed with benzene. Benzene was distilled off and the residue column chromatographed.

Elution with benzene-pet. ether (2:8) gave **4a** which crystallised from benzene-pet. ether as light yellow crystals (60 mg) m.p. 115-16°: R_f 0.54 (solvent-A) (Found: C, 78.9; H, 5.7. $C_{20}H_{18}O_3$ requires C, 78.4; H, 5.9%); UV: 273 (4.41) and 331 (4.48); IR: 1665, 1615 and 1595; 200 MHz PMR: 1.42 [*s*, 6H, $(CH_3)_2C<$], 390 (*t*, 1H, C_3-H), 4.69 (*d*, $J=9.5$ & 6.0 Hz, 2H, C_2-H_2), 5.50 (*d*, $J=9.5$ Hz, 1H, $C_{5'}$H), 6.50 (*d*, $J=9.5$ Hz, 1H, $C_{4'}$H), 6.61 (*d*, $J=9.5$ Hz, 1H, C_6-H), 7.35 (*s*, 5H, C_6H_5), and 7.79 (*d*, $J=9.5$ Hz, 1H, C_5-H); 50 MHz ^{13}C-NMR: 28.00 (*q*, $2\times CH_3$), 51.99 (*d*, C-3), 72.66 (*t*, C-2), 75.08 (*s*, C-6″), 108.70 (*s*, C-8), 113.4 (*d*, C-6), 115.72 (*d*, C-5″), 125.80 (*s*, C-4a), 127.04-128.86 (*m*, C-2′, C-3′, C-4′, C-5′, C-6′ and C-5 and C-4″), 135.54 (*s*, C-1′), 156.86 (*s*, C-8a), 159.56 (*s*, C-7), and 190.70 (*s*, CO).

Following compounds were also prepared and purified in a similar manner.

4′-Methoxy-6″,6″-dimethylpyrano[2″,3″:7,8]isoflavanone (**4b**):

Crystallized from hot pet. ether as colourless crystals (75 mg), m.p. 120-22°; R_f 0.58 (solvent-A) (Found: C, 74.6; H, 5.6. $C_{21}H_{20}O_4$ requires C, 75.00; H, 6.0%); UV: 267 (4.23) and 321 (4.2); IR: 1640, 1610 and 1590; 200 MHz PMR: 1.46 [*s*, 6H, $(CH_3)_2C<$], 3.80 (*s*, 3H, OCH_3), 4.08 (*t*, 1H, C_3-H), 4.52 (*d*, $J=6.0$ Hz, 2H, C_2-H_2), 5.50 (*d*, $J=9.5$ Hz, 1H, $C_{5'}$-H), 6.50 (*d*, $J=9.5$ Hz, 1H, C_6-H), 6.66 (*d*, $J=9.5$ Hz, 1H, $C_{4'}$H), 7.30 (*d*, $J=9.5$ Hz, 2H, $C_{3'}$H and $C_{5'}$H), 7.60 (*d*, $J=9.5$ Hz, 2H, $C_{2'}$H and $C_{6'}$H) and 7.84 (*d*, $J=9.5$ Hz, 1H, C_5-H).

2′,4′-Dimethoxy-6″,6″-dimethylpyrano[2″,3″:7,8]-*isoflavanone* (**4c**)

Crystallized from methanol as light yellow plates (80 mg), m.p. 112-14°; R_f 0.57 (solvent-B) (Found: C, 71.8; H, 6.4. $C_{22}H_{22}O_5$ requires C, 72.1; H, 6.1%); UV: 275 (4.47) and 311 (4.2); 200 MHz PMR: 1.43 [*s*, 6H, $(CH_3)_2C<$], 3.78 (*s*, 6H, $2\times OCH_3$), 4.16 (*dd*, 1H, C_3-H), 4.32 (2*dd*, 2H, C_2-H_2), 5.54 (*d*, J=9.5 Hz, 1H, $C_{5''}$-H), 6.42 (*m*, 3H, $C_{3'}$-H, C_5-H and C_6-H), 6.54 (*d*, J=9.5 Hz, 1H, $C_{4''}$-H), 7.00 (*d*, J=9.5 Hz, 1H, $C_{6'}$-H) and 7.74 (*d*, J=9.5 Hz, 1H, C_5-H); 50 MHz ^{13}C-NMR: 28.39 (*m*, $2\times CH_3$), 47.18 (*d*, C-3), 55.52 (*m*, $2\times OCH_3$), 71.27 (*t*, C-2), 76.20 (*s*, C-6″), 99.18 (*d*, C-6), 104.71 (*d*, C-5′), 108.10 (*s*, C-8), 110.91 (*d*, C-5″), 115.84 (*d*, C-3′), 121.84 (*s*, C-4a), 125.20 (*s*, C-1′), 128.49 (*d*, C-4″), 130.68 (*d*, C-5), 128.52 (*d*, C-6′), 157.7 (*s*, C-2′), 158.4 (*s*, C-4′), 159.0 (*s*, C-8a), 160.48 (*s*, C-7) and 191.4 (*s*, CO).

Second method

7-(1,1-Dimethylpropargyloxy)isoflavanone (**3a**, **3b** or **3c**) (0.5 mmol) was refluxed in N,N-dimethylaniline (5 ml) for 3.5 hr at 210-20° and the resulting solution poured over ice-cold dil. hydrochloric acid. The solid was collected and crystallied to give **4a-c**. The products **4a**, **4b** and **4c** agreed with the samples prepared above in m.p., UV, IR and PMR spectra.

2-Aryl-6,2′,4′-trihydroxybenzofuran (**7a**) and its derivatives (**7b** and **7c**)

2,4-Dihydroxy-2′,4′-dimethoxydesoxybenzoin (**5**, 500 mg) was intimately mixed with anhyd. pyridinium bromide (5 g) and the mixture heated carefully in a dry test tube until it melted. It was kept at this stage for 2 min, cooled to room temperature and the precipitated solid crystallized from methanol to give **7a** as buff coloured crystals (300 mg), m.p. 192-94°; R_f 0.31 (solvent-C) (Found: C, 69.8; H, 4.6. $C_{14}H_{10}O_4$ requires C, 69.4; H, 4.2%); UV: 280 (sh) (3.86), 320 (4.49) and 335 (4.47); IR: 3300(b), 1610, 1595, 1500, 1465 and 1440; 90 MHz PMR (acetone-d_6): 6.46 (*dd*, J=9.5 and 2.5 Hz, 2H, $C_{3'}$-H and $C_{5'}$-H), 6.72 (*dd*, J=9.5 and 2.5 Hz, 2H, C_5-H and C_7-H), 6.94 (*s*, 1H, C_3-H), 7.31 (*d*, J=9.5 Hz, 1H, C_6-H) and 7.67 (*d*, J=9.5 Hz, 1H, C_4-H); 50 MHz ^{13}C-NMR (acetone-d_6): 99.08 (*d*, C-3), 103.80 (*d*, C-7), 108.06 (*d*, C-5), 110.85 (*s*, C-3a), 112.37 (*d*, C-5′ and C-3′), 121.13 (*d*, C-4), 123.26 (*s*, C-1′), 127.88 (*d*, C-6′), 152.90, 155.40, 155.49, 155.60 and 158.83 (5*s*, C-2, C-6, C-7a, C-2′ and C-4′).

Its methyl ether (**7b**) was prepare by refluxing **7a** (242 mg, 1 mmol) in dry acetone (10 ml) with DMS (0.33 ml, 3.5 mmol) and anhyd. potassium carbonate (2.0 g) for 5 hr, and crystallized from benzene-pet. ether as colourless powder (250 mg), m.p. 84-85°; R_f 0.76 (solvent-B) (Found: C, 72.2; H, 6.1. $C_{17}H_{16}O_4$ requires C, 71.8, H, 5.7%); UV: 282 (sh) (3.89), 320 (4.50) and 335 (4.45); IR: 1600, 1590, 1460 and 1370; 90 MHz PMR: 3.75, 3.86 (2*s*, 9H, $3\times OCH_3$), 6.50 (*dd*, J=9.5 Hz and 2.5 Hz, 2H, $C_{2'}$-H and $C_{5'}$-H), 6.70 (*dd*, J=9.5 and 2.5 Hz, 1H, C_5-H), 6.96 (*d*, J=2.5 Hz, 1H, C_7-H), 7.03 (*s*, 1H, C_3-H), 7.36 (*d*, J=9.5 Hz, 1H, $C_{6'}$-H) and 7.80 (*d*, J=9.5 Hz, 1H, C_4-H).

The acetate (**7c**) was obtained by refluxing **7a** with acetic anhydride-pyridine for 45 min, and crystallized from methanol as light cream coloured solid, m.p. 138-39°; R_f 0.59 (solvent-B) (Found: C, 64.7, H, 4.8. $C_{20}H_{16}O_7$ requires C, 65.2 H, 4.4%); UV: 279 (sh) (4.1), 304 (4.53) and 316 (4.45); IR: 1760, 1605, 1590 and 1455; 90 MHz PMR: 2.25, 2.27 and 2.35 (3*s*, 9H, $3\times OCOCH_3$), 6.96-7.05 (*m*, 4H, $C_{3'}$-H, $C_{5'}$-H, C_5-H and C_7-H), 7.20 (*s*, 1H, C_3-H), 7.55 (*d*, J=9.5 Hz, 1H, $C_{6'}$-H) and 7.95 (*d*, J=9.5 Hz, 1H, C_4-H).

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Application of Phase-Transfer Catalysis to the Synthesis of Mono- & Bis-stilbenes & Styryls

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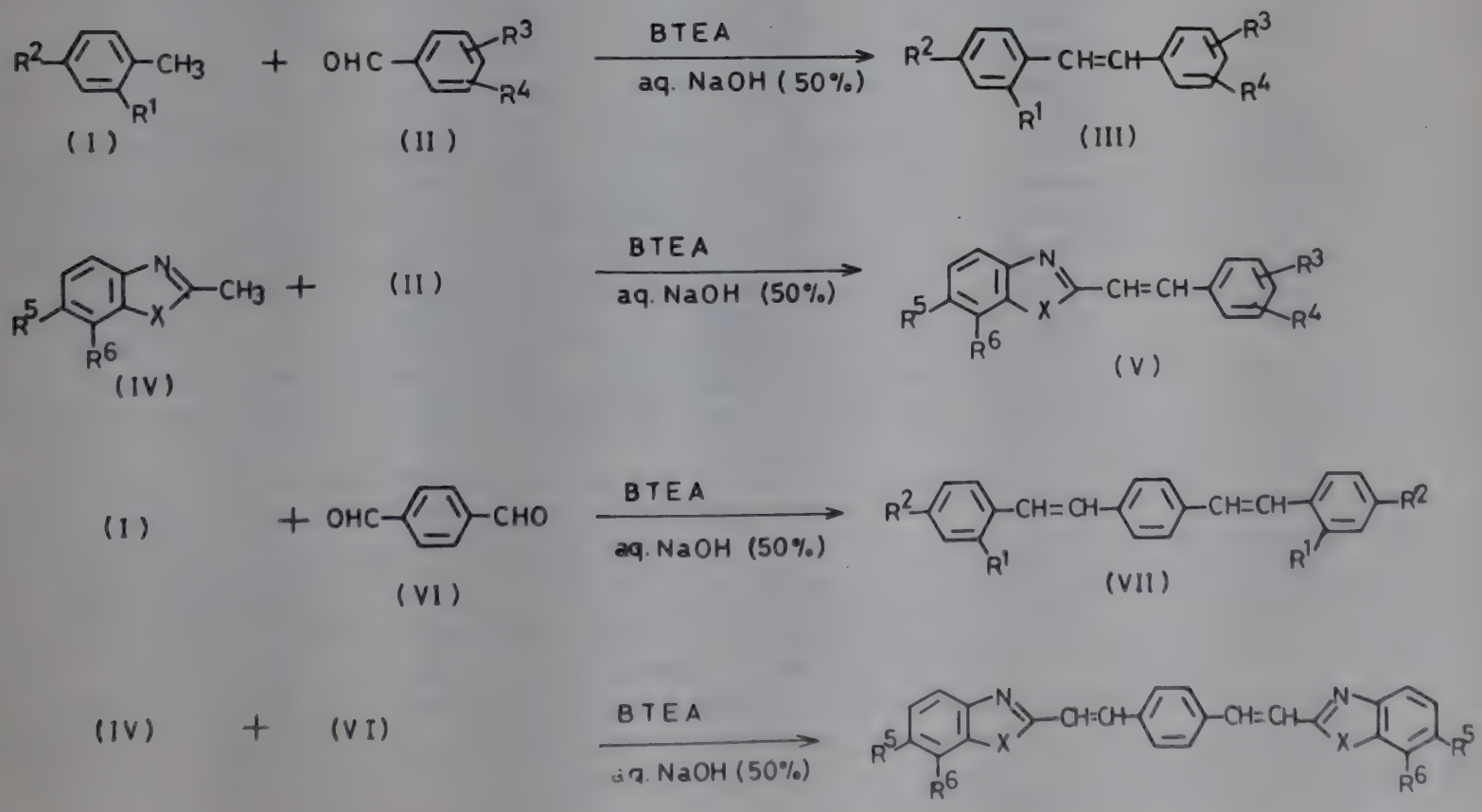
A novel and convenient method has been developed for the synthesis of substituted stilbenes by the condensation of active methyl group in suitably substituted toluenes with aromatic aldehydes in aq. medium at room temperature using benzyltriethylammonium chloride as a phase-transfer catalyst. This method has also been applied for the preparation of heterocyclic styryls and extended to the synthesis of bis-stilbenes and bis-styryls using aromatic dialdehydes in place of monoaldehydes. A comparison of the results shows that the present method is superior to the conventional methods in many respect.

Many heterogeneous reactions and the reactions which are traditionally carried out in non-aqueous media are simplified and rendered fast by the use of phase-transfer catalysis (PTC). This technique has been successfully applied to a wide spectrum of organic reactions such as carbene reactions[1], nucleophilic substitution[2], elimination[3], alkylation[4], acylation[5], hydrolysis of esters[1], oxidation of alkenes[6], borohydrate reduction[7], dueterium and oxygen exchange reactions[1,8], etc. It was our interest to extend the application of this promising method to the synthesis of mono- and bis-stilbenes and styryls which form a group of important inter-mediates for dyes and optical brighteners. It was therefore envisaged to synthesise mono- and bis-stilbenes by the condensation of toluenes containing an electron withdrawing group such as nitro, cyano and halogen in *ortho*, or *para*-position with respect to methyl group, with benzaldehyde derivatives or with terephthalaldehyde in aq. alkaline medium using benzyltriethylammonium chloride (BTEA) as a phase-transfer catalyst. It was also envisaged to synthesise heterocyclic mono- and bis-styryls by the condensation of 2-methylheterocycles with benzaldehydes or with terephthalaldehyde using PTC.

The reaction between the substituted toluene (I) or 2-



SCHEME 1

methylheterocycle (IV) and benzaldehyde (II) or terephthaldehyde (VI) (Scheme 1) in stoichiometric proportions was carried out at room temperature under aq. alkaline condition using a catalytic amount of phase-transfer catalyst BTEA. The mono- and bis-stilbenes and styryls were isolated by dilution of the reaction mixture, neutralisation with dil. hydrochloric acid and filtration of the solid obtained. Their characterization data are given in Table 1. Some mono-stilbenes and styryls were also prepared following conventional methods and the results compared with those of PTC technique (Table 2).

In the preparation of mono-stilbenes employing PTC technique, *p*-nitrotoluene was found to be more reactive than *p*-cyanotoluene and 2,4-dinitrotoluene to be the most reactive compound among the toluene derivatives used in the present work. Also, the chloronitrotoluenes were found to be more reactive

Table 1—Reaction Periods for the Formation of Substituted Mono-stilbenes (III), Heterocyclic Mono-styryls (V), Bis-stilbenes (VII) and Heterocyclic Bis-styryls (VIII) and Their Characterization Data

Compd	R^1	R^2	R^3	R^4	R^5	R^6	X	Reaction Period	m.p.* °C	Yield (%)	Mol. Formula†
III_1	H	NO_2	H	H	—	—	—	5	159	78	$C_{14}H_{11}NO_2$
III_2	H	NO_2	4-Cl	H	—	—	—	4	185-86	86	$C_{14}H_{10}NO_2Cl$
III_3	H	NO_2	4-NO_2	H	—	—	—	4.5	294-95	85	$C_{14}H_{10}N_2O_4$
III_4	H	NO_2	4-MeO–	H	—	—	—	8	133	85	$C_{15}H_{13}NO_3$
III_5	H	NO_2	4-$(H_3C)_2N$–	H	—	—	—	4.5	252	76	$C_{16}H_{16}N_2O_2$
III_6	CN	NO_2	H	H	—	—	—	3	176-78	88	$C_{15}H_{10}N_2O_2$
III_7	CN	NO_2	4-Cl	H	—	—	—	1.5	195-97	94	$C_{15}H_9N_2O_2Cl$
III_8	CN	NO_2	4-MeO–	H	—	—	—	6	198	80	$C_{16}H_{12}N_2O_3$
III_9	CN	NO_2	2-MeO–	4-MeO	—	—	—	10	163	62	C_1-$H_{14}N_2O_4$
III_{10}	CN	NO_2	4-$(CH_3)_2N$–	H	—	—	—	4	209	96	$C_{17}H_{15}N_2O_2$
III_{11}	H	CN	4-NO_2	H	—	—	—	5	349	76	$C_{15}H_{10}N_2O_2$
III_{12}	NO_2	CN	4-MeO	H	—	—	—	7	159	73	$C_{16}H_{12}N_2O_3$
III_{13}	NO_2	NO_2	H	H	—	—	—	1	194	92	$C_{14}H_{10}N_2O_4$
III_{14}	NO_2	Cl	4-$(CH_3)_2N$–	H	—	—	—	3.5	151-52	95	$C_{16}H_{14}N_2Cl$
III_{15}	Cl	NO_2	4-$(CH_3)_2N$–	H	—	—	—	3	193	98	$C_{16}H_{15}N_2O_2Cl$
V_1	—	—	H	H	H	H	S	4.5	112	72	$C_{15}H_{11}NS$
V_2	—	—	2-Cl	H	H	H	S	6	164-65	75	$C_{15}H_{10}NSCl$
V_3	—	—	4-NO_2	H	H	H	S	2	229	88	$C_{15}H_{10}N_2O_2S$
V_4	—	—	4-MeO	H	H	H	S	10	145	80	$C_{16}H_{13}NOS$
V_5	—	—	2-MeO	3-MeO	H	H	S	14	90-91	69	$C_{17}H_{15}NO_2S$
V_6	—	—	H	H	H	H	O	6.5	84-85	70	$C_{15}H_{11}NO$
V_7	—	—	4-Cl	H	H	H	O	3.5	144-45	85	$C_{15}H_{10}NOCl$
V_8	—	—	4-NO_2	H	H	H	O	4.5	240	91	$C_{15}H_{10}N_2O_3$
V_9	—	—	4-MeO–	H	H	H	O	12	137-38	74	$C_{16}H_{13}NO_2$
V_{10}	—	—	3-MeO	4-MeO	H	H	O	15	129	83	C_1-$H_{15}NO_3$
V_{11}	—	—	H	H	H	H	NH	8	201-02	58	$C_{15}H_{12}N_2$
V_{12}	—	—	4-Cl	H	H	H	NH	6	224-25	76	$C_{15}H_{11}N_2Cl$
V_{13}	—	—	4-NO_2	H	H	H	NH	6.5	266	72	$C_{15}H_{10}N_3O_2$
V_{14}	—	—	4-MeO–	H	H	H	NH	16	216	52	$C_{16}H_{13}N_2O$
V_{15}	—	—	2-MeO–	3-MeO–	H	H	NH	20	170-71	49	C_1-$H_{16}N_2O_2$
V_{16}	—	—	H	H	Benzo		O	6	122-23	77	$C_{18}H_{13}NO$
V_{17}	—	—	4-Cl	H	Benzo		O	3.5	164	92	$C_{18}H_{12}NOCl$
V_{18}	—	—	2-Cl	H	Benzo		O	7	161	87	$C_{19}H_{12}NOCl$
V_{19}	—	—	4-NO_2	H	Benzo		O	4	242-43	89	$C_{18}H_{12}N_2O_3$
V_{20}	—	—	4-AcNH–	H	Benzo		O	10	239	73	$C_{20}H_{16}N_2O_2$
VII_1	H	NO_2	—	—	—	—	—	5	289	92	$C_{22}H_{16}N_2O_4$
VII_2	H	CN	—	—	—	—	—	5	277-78	18	$C_{24}H_{16}N_2$
VII_3	CN	H	—	—	—	—	—	8	228-29	12	$C_{24}H_{16}N_2$
VII_4	CN	NO_2	—	—	—	—	—	6	>340	66	$C_{24}H_{16}N_4O_4$
VII_5	NO_2	NO_2	—	—	—	—	—	2	294	97	$C_{24}H_{16}N_4O_8$
$VIII_1$	—	—	—	—	H	H	S	5	292	89	$C_{24}H_{16}N_2S_2$
$VIII_2$	—	—	—	—	H	H	O	3.5	336	81	$C_{24}H_{16}N_2O_2$
$VIII_3$	—	—	—	—	H	H	NH	8	>340	74	$C_{24}H_{18}N_4$
$VIII_4$	—	—	—	—	Benzo		O	6	265-66	84	$C_{32}H_{24}N_2O_2$

*Melting points are uncorrected.

†All compounds gave satisfactory elemental analyses.

Table 2—Comparison of Results Obtained from the Conventional Methods with Those from PTC Technique in the Synthesis of Stilbenes (III) and Styryls (V)

Compd	Results of the Conventional methods			Results of the PTC technique under alkaline medium		
	Experimental conditions	m.p. °C	Yield (%)	Experimental conditions	m.p. °C	Yield (%)
III_1	Arylsulphonamide catalyst, alk. medium, at 60° for 58 hr	158-59	73	0.1mol BTEA, 5 hr at room temperature	159	78
III_3	Meerwein arylation	294-95	11	0.01mol BTEA, 4.5 hr at room temperature	294-95	85
III_4	Wittig reaction	131-33	87	0.1mol BTEA, 8 hr at room temperature	132-33	85
III_{10}	Piperidine catalyst, 2.8 hr at 120-130°	209-10	36	0.1 mol BTEA, 4 hr at room temperature	210	96
III_{14}	Piperidine catalyst, 8 hr at 165-175°	151-52	40	0.1 mol BTEA, 3.5 hr at room temperature	151-52	95
V_1	Zinc chloride catalyst, 10 hr at 100°	111-12	38	0.15 mol BTEA, 4.5 hr at room temperature	111-12	72
V_4	Acetic anhydride catalyst, 24 hr at 120°	145	43	0.15 mol BTEA, 10 hr at room temperature	145	80
V_6	Potassium methoxide catalyst, 7 hr at reflux	84-85	6.9	0.15 mol BTEA, 6.5 hr at room temperature	84-85	70
V_7	Boric acid catalyst, 5 hr at 200°	143-45	50	0.15 mol BTEA, 3.5 hr at room temperature	144-45	85
V_{13}	Without any catalyst, 8 hr at 210°	264-65	70	0.20 mol BTEA, 6.5 hr at room temperature	266	72
V_{17}	*p*-Toluenesulphonamide and DMF as catalysts in xylene, 48 hr at reflux	163-64	91	0.15 mol BTEA, 3.5 hr at room temperature	164	92

than *p*-nitrotoluene. This observation is in agreement with that of Chardonnens[9] who carried out these reactions by conventional methods. Condensation using only *p*-cyanotoluene gave a side product (20%) identified as *p*-toluic acid. The amount of catalyst BTEA required in the case of mono-stilbenes was found to be 0.1 mol. Mono-stilbenes (III) were obtained in very good yields (62-98%; Table 1).

In the preparation of heterocyclic mono-styryls (V), the reaction of 2-methylbenzothiazole was fastest among the heterocyclic compounds used. However, the reaction of 2-methylbenzimidazole was slowest and gave styrylbenzimidazoles in very poor yields. The yield was, however, improved in the case of styrylbenzimidazoles by increasing the molar proportions of BTEA from 0.15 (normally found suitable for other 2-methylheterocyclic compounds) to 0.2. Among the aromatic aldehydes used, *p*-methoxybenzaldehyde and dimethoxybenzaldehydes showed slower rates of reaction with the formation of side products. The side product in each case was soluble in alkali and was converted into the corresponding styryl compound by heating in a boiling mixture of acetic acid-sulphuric acid (1 : 1). Except mono-styrylbenzimidazoles (V_{12}-V_{15}) which were obtained in fairly good yields (50-75%), the yields of other heterocyclic mono-styryls (V_1-V_{10} and V_{16}-V_{20}) were high (70-90%; Table 1).

In the preparation of bis-stilbenes (VII) and heterocyclic bis-styryls (VIII), the optimum molar proportion of BTEA per mol of terephthalaldehyde was found to be 0.3. Satisfactory results were obtained by raising the temperature to 45°C as compared to the reaction conducted at room temperature. The yields of pure bis-stilbenes were excellent (92-97%) except when cyanotoluenes were used. The poor yields (12-

18%) from *o*- and *p*-cyanotoluenes and the relatively lower yields (66%) from 2-cyano-4-nitrotoluene can be explained on the basis of hydrolysis of cyano compounds to the corresponding water soluble carboxylic acids under aq. alkaline condition and the raised reaction temperature. The yields of pure heterocyclic bis-styryls were excellent (81-89%). However, the slightly lower yield (74%) of $VIII_3$ is in agreement with the lower yields of all the mono-styryls (V_{11}-V_{15}) derived from the same heterocyclic compound 2-methylbenzimidazole. The yield of $VIII_3$ however, could not be increased further by increasing either the molar proportion of BTEA or the reaction temperature.

A comparison of the results of PTC technique with those of conventional methods (Table 2) shows that the former technique is superior. Other merits of the PTC technique are the milder reaction conditions, simple method for isolation of the products, higher purity and very good yields of the products, shorter reaction period, and no use of a solvent or strict maintenance of anhydrous conditions.

Experimental Procedure

Benzyltriethylammonium chloride (BTEA) was prepared by refluxing one mol of benzyl chloride with 1.1 mol of triethylamine in dry benzene. The white product separated was isolated by filtration in nearly quantitative yield.

Substituted mono-stilbenes (III; Table 1) using PTC: General procedure

A suitably substituted toluene derivative (I; 0.01 mol) was mixed with an aromatic aldehyde (II; 0.01 mol) and BTEA (0.23 g, 0.001 mol) and the mixture stirred. A small quantity of water (about 2 ml) was then added, if necessary, to facilitate the stirring. Highly concentrated aq. sodium hydroxide solution (3 to 5 ml) was added dropwise during 30-45 min and at the end of the addition the concentration of sodium hydroxide solution adjusted to 50% taking into account the quantity of previously added water. The mixture was stirred at room temperature till the reaction was complete (1-10 hr; monitored by TLC). The reaction mixture was diluted with water, neutralised with dil. hydrochloric acid (*pH* 8-8.5), the product filtered, washed with water, dried and crystallised from ethanol.

Substituted mono-styryls (V; Table 1) using PTC: General procedure

The appropriate 2-methylbenzazole (IV; 0.01 mol) was mixed with an aromatic aldehyde (0.01 mol) and BTEA (0.34 g, 0.0014 mol) and the mixture stirred. Only in the case of 2-methylbenzimidazole higher proportion of BTEA (0.46 g, 0.002 mol) was required. The reaction was carried out using 50% aq. sodium hydroxide solution and the isolation of the products was followed in the same manner as in the above procedure for III, except that the completion of reaction required a longer period (2-20 hr; monitored by TLC).

Substituted bis-stilbenes (VI) and heterocyclic bis-styryls (VIII) (Table 1): General procedure

A suitably substituted toluene derivative (I; 0.02 mol) or a suitable 2-methylbenzazole (IV; 0.02 mol) was mixed with terephthalaldehyde (VI; 1.34 g, 0.01 mol) and BTEA (0.68 g, 0.003 mol) and the mixture stirred. The reaction was carried out using 50% aq. sodium hydroxide solution at 45° for 2-20 hr (monitored by TLC). The products were isolated in the same manner as in the above procedure for III, and crystallised from ethanol and dimethylformamide.

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A New Synthesis of 1,3,4-Thiadiazolo[2,3-*b*]quinazolin-5-ones

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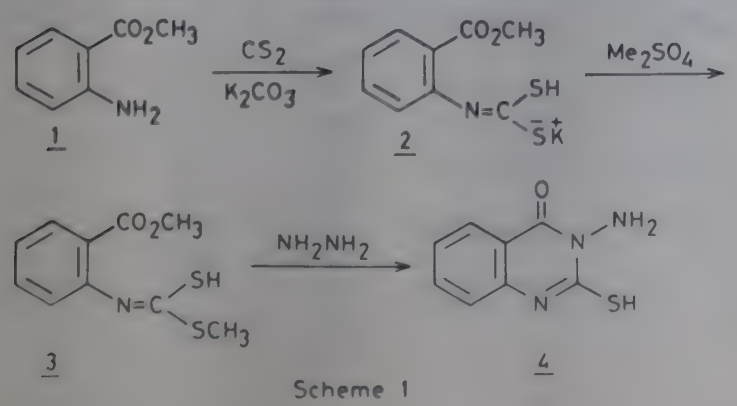
A new synthesis of 3-amino-2-mercaptoquinazolin-4-one (**4**) and its cyclization to thiadiazoloquinazolines by reaction with one carbon donors is reported.

A variety of useful biological activities encountered in quinazolin-4-one derivatives have given an impetus to the synthesis of the condensed quinazolin-4-ones. Among the various such systems that have been synthesized so far, 1,3,4-thiadiazolo[2,3-*b*]quinazolin-5-one derivatives received only a scanty attention[1-3]. It was, therefore, thought of interest to synthesise these condensed quinazolone derivatives for pharmacological screening.

Earlier, Russo *et al.*[1] have synthesised a few thiadiazoloquinazolines by fusing methyl anthranilate with chlorothiazole derivatives. Our approach to the synthesis of 2-substituted thiadiazolo[2,3-*b*]quinazolin-5-ones involved building of a thiadiazole ring on a quinazoline ring.

3-Amino-2-mercaptoquinazolin-4-one (**4**) has been synthesised from *o*-methoxycarbonylphenyl isothiocyanate by reaction[4] with hydrazine hydrate as well as by the hydrolysis[5] of 3-acetylamino-2-mercaptoquinazolin-4-one. In the present study an alternative approach was employed for the synthesis of **4**. It involved the reaction of methyl anthranilate (**1**) with carbon disulphide followed by methylation with dimethyl sulphate to give the methyl dithiocarbonate (**3**) and stirring of **3** with hydrazine hydrate (80%) (Scheme 1).

The desired 1,3,4-thiadiazolo[2,3,-*b*]quinazolin-5-ones were obtained by the reaction of **4** with one carbon donors. Thus, **4** when reacted with triethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulphonic acid gave thiadiazolo[2,3-*b*]quinazolin-5-one (**5**). However, this compound (**5**) could not be obtained by refluxing **4** with formic acid.



1 2 3 4

Scheme 1

The base-catalysed condensation of **4** with carbon disulphide yielded 2-mercaptothiadiazoloquinazolin-5-one (**6**). Methylation of **6** with dimethyl sulphate gave the methylthio-derivative (**7**) which underwent nucleophilic displacement of methylthio group with morpholine to yield expected 2-(4-morpholinyl)-thiadiazoloquinazolin-5-one (**8**).

All attemptes to prepare 2-amino-, 2-alkylamino- and 2-arylamino-thiadiazoloquinazolines from **7** by reaction with ammonia, alkyl and arylamines were not successful. However, 2-aminothiadiazoloquinazolin-5-one (**9**) could be prepared by the direct cyclization of **4** with cyanogen bromide.

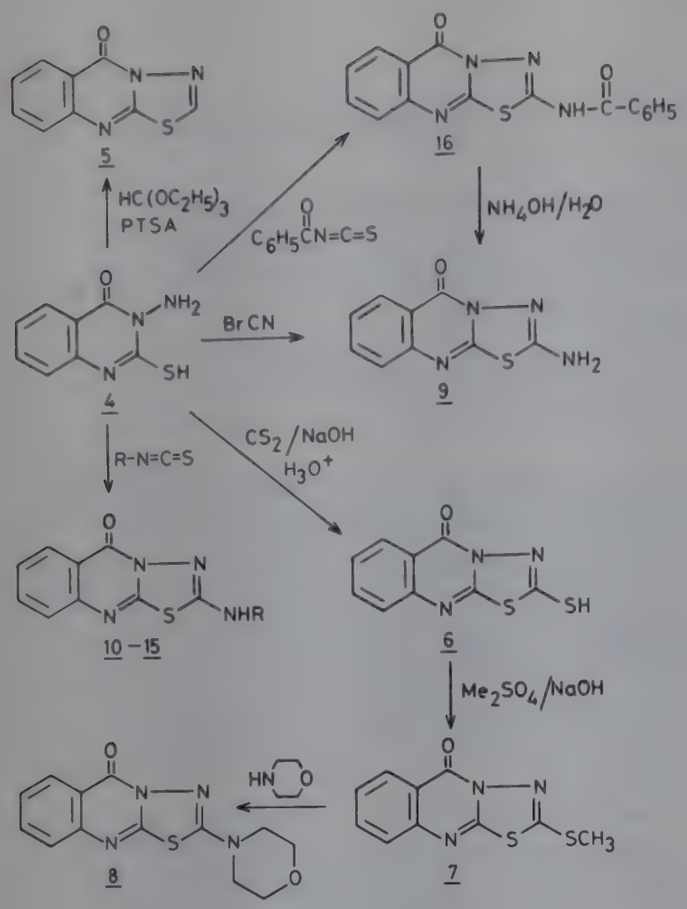
The condensation of **4** with alkyl, aryl and benzoyl isothiocyanates afforded the corresponding 2-substituted aminothiadiazoloquinazolines (**10-16**). Further, the base-catalysed hydrolysis of 2-benzoylamino derivatives (**16**) yielded 2-aminothiadiazoloquinazolin-5-one (**9**) (Scheme 2) (Table 1).

Attempts to cyclize **4** with acetic anhydride, ethyl chloroformate, aliphatic or aromatic nitriles under acidic as well as basic conditions, however, did not meet with success.

Thiadiazoloquinazolines exhibited characteristic UV absorptions around 285 and 334 nm. In the IR spectra the $\nu C=O$ band of the thiadiazoloquinazolines appeared around 1680 cm^{-1}. The aminothiadiazoloquinazolines (**8-16**) also exhibited the NH stretching absorptions in the region 3300-3500 cm^{-1}.

Experimental Procedure

Melting points are uncorrected. UV spectra were determined in abs. ethanol on a Beckman DK 24 spectrophotometer, IR spectra in nujol on a Perkin-Elmer model 157 spectrophotometer, and mass spectra on a Varian-Atlas CH-7 mass spectrometer at 70 eV ionizing beam.



Scheme 2

3-Amino-2-mercaptoquinazolin-4-one (**4**)

A mixture of methyl anthranilate (30 g; 0.2 mol), carbon disulphide (20 ml) and potassium carbonate (60 gm was stirred for 12 hr at room temperature. The reaction mixture was heated further on a water-bath for 12 hr, cooled and poured into ice-water. The unreacted methyl anthranilate (7 g) was separated and the aq. phase was treated dropwise, with dimethyl sulphate (30 ml) under stirring. The reaction mixture was allowed to stand at room temperature for 12 hr and extracted with chloroform. The solvent was removed by distillation under reduced pressure, and the crude methyl *o*-methoxycarbonylphenyldithiocarbonate (**3**), obtained on cooling, was treated dropwise with hydrazine hydrate (80%, 20 ml). The mixture was stirred for 30 min at room temperature and poured into ice-water. The solid obtained was filtered, washed with water, dried and recrystallized from dimethylformamide-ethanol to give **4**, yield 12.5 g (43%), m.p. 236-37° (lit.[4], m.p. 236-37°).

1,3,4-*Thiadiazolo*[2,3-*b*]*quinazolin*-5-*one* (**5**)

A mixture of **4** (3.68 g; 0.02 mol) and *p*-toluenesulphonic acid (20 mg) in excess of triethyl orthoformate (25 ml) was refluxed for 6 hr and excess of triethyl orthoformate removed under reduced

Table 1—Characterization Data of Various 1,3,4-Thiadiazolo[2,3-*b*]quinazolin-5-ones Prepared

Compd	R	Yield (%)	Crystallized from	m.p.° °C	Mol. formula	Found (%) (Calc.) C	H
5	—	69	Chloroform	232-34 (245)[1]	$C_9H_5N_3OS$	53.5 (53.2	2.7 2.5)
6	—	64	Methanol	274-78	$C_9H_5N_3OS_2$	46.0 (45.9	2.1 2.1)
7	—	82	Methanol	210-11 (210-12)[1]	$C_{10}H_7N_3OS_2$	48.5 (48.2	3.1 2.8)
8	—	66	DMF-EtOH	274-76	$C_{13}H_{12}N_4O_2S$	54.1 (54.2	4.1 4.2)
9	—	92	DMF-EtOH	324-25 (322-25)[1]	$C_9H_6N_4OS$	49.8 (49.5	3.0 2.8)
10	CH_3NH	43	Methanol	244-46	$C_{10}H_8N_4OS$	51.8 (51.7	3.8 3.5)
11	$CH_3(CH_2)_3NH-$	63	DMF-EtOH	219-21	$C_{13}H_{14}N_4OS$	57.2 (56.9	5.6 5.1)
12	$C_6H_5CH_2NH-$	49	Methanol	274-76	$C_{16}H_{12}N_4OS$	62.0 (62.3	4.0 3.9)
13	C_6H_5NH-	71	Methanol	294-96	$C_{15}H_{10}N_4OS$	61.5 (61.2	3.8 3.4)
14	$3\text{-}CH_3C_6H_4NH-$	65	Methanol	299-301	$C_{16}H_{12}N_4OS$	62.5 (62.3	4.0 3.9)
15	$4\text{-}ClC_6H_4NH-$	62	Methanol	333-35	$C_{15}H_9N_4OSCl$	55.0 (54.8	3.0 2.8)
16	—	69	DMF-EtOH	332-34	$C_{16}H_{10}N_4O_2S$	59.7 (59.6	3.3 3.1)

*Literature values are given in parentheses.

pressure. The solid obtained was crystallized from chloroform to give **5** (Table 1).

2-*Mercapto*-1,3,4-*thiadiazolo*[2,3-*b*]*quinazolin*-5-*one* (**6**)

A mixture of **4** (3.86 g; 0.02 mol), sodium hydroxide (0.8 g; 0.02 mol) in water (25 ml) and carbon disulphide (1.52 g; 0.02 mol) was heated on a water-bath for 6 hr. The aqueous layer was filtered, cooled and acidified with dilute hydrochloric acid (10%). The solid obtained was filtered, washed with water, dried and recrystallized from methanol to give **6** (Table 1).

2-*Methylthio*-1,3,4-*thiadiazolo*[2,3-*b*]*quinazolin*-5-*one* (**7**)

To an ice-cold solution of **6** (4.7 g; 0.02 mol) in 2% aq. sodium hydroxide solution (40 ml) was added dropwise, with stirring, dimethyl sulphate (2.77 g; 0.02 mol). The mixture was stirred for 4 hr at room temperature. The solid obtained was filtered, washed with cold water, dried and recrystallized from methanol to yield **7** (Table 1).

2-*Morpholino*-1,3,4-*thiadiazolo*[2,3-*b*]*quinazolin*-5-*one* (**8**)

A mixture of **7** (2.49 g; 0.01 mol) and morpholine (10 ml) was refluxed for 6 hr. The reaction mixture was chilled, and the resultant solid filtered, washed with water, dried and recrystallized from dimethylformamide-ethanol to yield **8** (Table 1).

2-*Amino*-1,3,4-*thiadiazolo*[2,3-*b*]*quinazolin*-5-*one* (**9**)

A solution of cyanogen bromide (1.15 g; 0.011 mol) in ethanol was added dropwise to a stirred suspension of **4** (1.93 g; 0.01 mol) in ethanol (25 ml). The mixture was stirred for 4 hr at room temperature. The solid obtained was filtered, washed with water, dried and recrystallized from dimethylformamide-ethanol to yield **9** (Table 1).

2-*Phenylamino*-1,3,4-*thiadiazolo*[2,3-*b*]*quinazolin*-5-*one* (**13**)

A mixture of **4** (3.86 g; 0.02 mol) and phenyl isothiocyanate (2.7 g; 0.02 mol) in dioxane (25 ml) was refluxed for 8 hr. The solvent was distilled under reduced pressure and the solid obtained crystallized from ethanol to yield **13** (Table 1).

Similarly prepared were the 2-substituted amino-1,3,4-thiadiazolo [2,3-*b*]quinazolin-5-ones (**10-12**, **14** and **15**; Table 1).

2-*Benzoylamino*-1,3,4-*thiadiazolo*[2,3-*b*]*quinazolin*-5-*one* (**16**)

To a stirred solution of ammonium thiocyanate (2.3 g; 0.03 mol) in acetone (15 ml) was added dropwise, benzoyl chloride (2.82 g; 0.02 mol). The mixture was stirred for 15 min and treated with a suspension of **4** (3.86 g; 0.02 mol) in acetone (100 ml). The mixture was refluxed for 3 hr, excess of acetone distilled off, and the residue poured into ice-water. The resultant solid was filtered, washed successively with sodium bicarbonate solution and water, dried and the crude mass extracted with hot benzene. The undissolved solid was dried and recrystallized from dimethylformamide-ethanol to yield **16** (Table 1).

2-*Amino*-1,3,4-*thiadiazolo*[2,3-*b*]*quinazolin*- 5-*one* (**9**)

A suspension of **16** (3.22 g; 0.01 mol) in 25% aq. ammonia solution (25 ml) was stirred at room temperature for 48 hr. The solid obtained was filtered, washed with water, dried and recrystallized from dimethylformamide-ethanol to yield **9** (Table 1).

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[1,3] Dioxolo[4,5-*g*]thiazolo[3,2-*a*]quinazolin-5-ones

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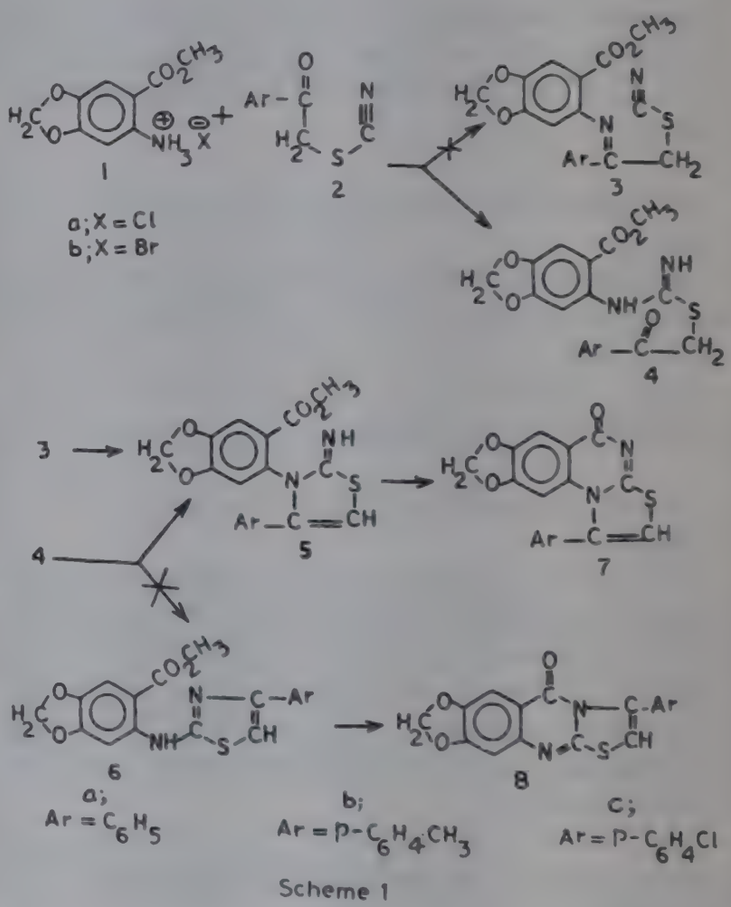
Some [1,3]dioxolo[4,5-*g*]thiazolo[3,2-*a*]quinazolin-5-ones (**7**) with aryl substituents at position-1 have been synthesised by the condensation of methyl 6-aminopiperonylate hydrochloride (**1a**) with α-thiocyanoketones (**2**). Also, 1,2-dihydro-5*H*-[1,3]dioxolo[4,5-*g*]thiazolo[3,2-*a*]quinazolin-5-one (**16**) has been synthesised by the condensation of methyl 6-aminopiperonylate hydrobromide (**1b**) with β-bromoethylthiocyanate (**11**), or by the condensation of methyl 6-thiocyanatoaminopiperonylate (**9**) with 1,2-dibromoethane (**10**). The structure (**16**) has been supported by PMR data and by preparing its linear isomer, 7,8-dihydro-10*H*-[1,3]dioxolo[4,5-*g*]thiazolo[2,3-*b*]quinazolin-10-one (**17**) unambiguously by the condensation of methyl 6-aminopiperonylate (**1**) with 2-bromothiazoline hydrobromide (**19**).

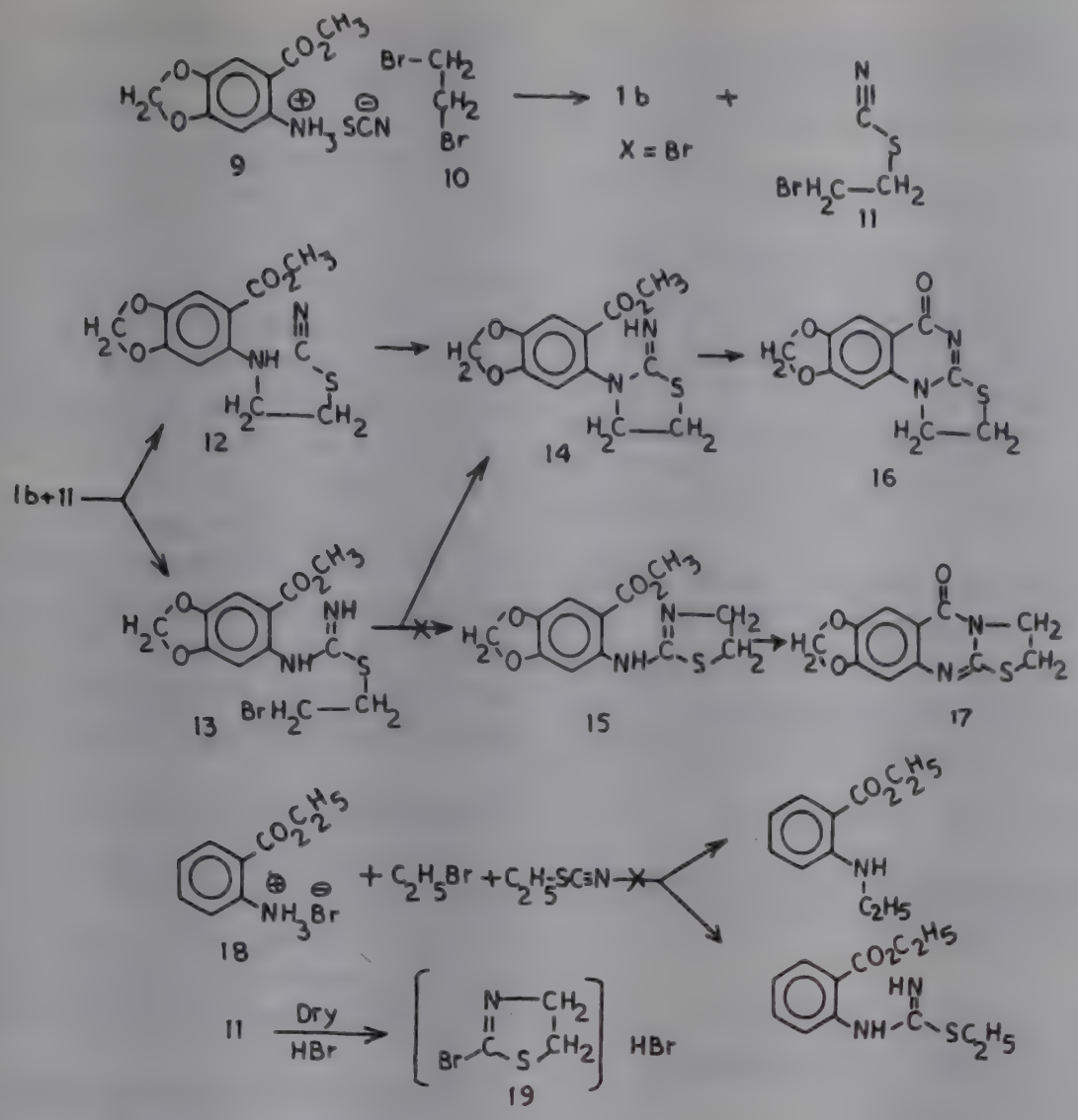
Sharma *et al.*[1] reported the synthesis of some 8-arylsubstituted-1,3-dioxolo[4,5-*g*]thiazolo [2,3-*b*]quinazolin-10-ones (**8**). It was thought desirable to synthesise the isomeric angular compounds 5*H*-1,3-dioxolo[4,5-*g*]thiazolo [3,2-*a*]quinazolin-5-ones (**7**) with substitution at position-1. For this, we started with the method very often used in our laboratories[2-4]. Condensation of methyl 6-aminopiperonylate hydrochloride (**1a**) with various α-thiocyanoketones (**2**) could give rise to angular product (**7**) or linear product (**8**) or to both **7** and **8**, depending upon the mode of cyclisation of the intermediates **3** or **4** (see Scheme 1). But in these reactions, we obtained only a single product in each case as revealed by TLC. That the products are **7** was evident from their PMR spectra and the fact that these products differed (m.ps, R_f values and PMR spectra) from the corresponding linear product (**8**) obtained by Sharma *et al.*[1]. For example the PMR spectrum of **7a** exhibited a multiplet (7H) at δ 7.46-7.86 assignable to aromatic protons, a singlet (1H) at 6.66 assignable to one vinylic proton (=C*H*−S−) and another singlet (2H) at 6.27 assignable to two methylenedioxy protons (−OCH_2O−). In the PMR spectrum of **8** (Ar=C_6H_5) the methylenedioxy protons (−OCH_2O−) appeared upfield at δ 5.90. This slight downfield shift of the methylenedioxy protons in the case of angular isomer (δ 6.27) may be attributed to the proximity effect of the aromatic nucleus.

That the thiazole ring (**5**) is formed prior to the formation of the pyrimidine ring (**7**) is supported by our earlier observations[5,6]. The work on the synthesis of **7** by an unamviguous route is in hand.

Further, it was thought appropriate to synthesise the dihydro derivative (**16**) also. This could be synthesised by the condensation of methyl 6-thiocyanato-aminopiperonylate (**9**) with 1,2-dibromoethane (**10**), or by the condensation of methyl 6-aminopiperonylate hydrobromide (**1b**) with β-bromoethylthiocyanate (**11**) (Scheme 2). In the condensation of **9** with **10**, **1b** and **11** could be isolated which further reacted to give rise to the final product. The first step would be the formation of intermediate (**12**) or (**13**). While the former (**12**) could give rise to angular product (**16**) only via **14**, the latter i.e. **13** could give rise to angular product **16** via **14** or linear one (**17**) via **15**, or it could give rise to both **16** and **17** depending upon mode of cyclisation. But in our hands only the angular product (**16**) was obtained. In order to establish whether the reaction proceeded via



Scheme 1



Scheme 2

the intermediate (**12**) or (**13**), we carried out the reaction of ethyl anthranilate hydrobromide (**18**; 0.01 mol) with ethyl thiocyanate (0.01 mol) and ethyl bromide (0.01 mol) in ethanol at room temperature. But the reaction did not take place even by keeping the reaction mixture at room temperature for 20 days. Efforts are under way to establish the reaction mechanism.

In order to confirm the structure of the final product, the PMR spectrum of **16** was not of much help to us. So we thought of an indirect evidence, i.e. we synthesised **17** by an unambiguous route involving condensation of methyl 6-aminopiperonylate (**1**) with 2-bromothiazoline hydrobromide (**19**), the latter in turn could be prepared by passing dry hydrobromic acid gas through the ethereal solution of **11**. Compound (**17**) prepared thus differed from **16** prepared by the condensation of **1b** and **11** in its melting point and TLC behaviour. Thus by the process of elimination, structure (**16**) to the condensation product of **1b** and **11** is justified.

Experimental Procedure

Melting points were determined in open glass capillaries in a liquid paraffin bath and are uncorrected. IR spectra were recorded in nujol on Perkin-Elmer 337 and 621 spectrophotometer and PMR on a Varian EM-390 90 MHz spectrometer using TMS as an internal reference.

Methyl 6-aminopiperonylate hydrochloride (**1a**) was prepared as usual from methyl 6-aminopiperonylate[7] and crystallised from ethanol, m.p. 197°; yield 3.20 g (90%).

1-Phenyl-5H-1,3-dioxolo[4,5-g]thiazolo[3,2-a]quinazolin-5-one (**7a**)

A solution of α-thiocyanoacetophenone[8] (**2**; Ar = C_6H_5; 0.88 g; 0.005 mol) in absolute ethanol (8 ml) was mixed with a solution of **1a** (1.15 g; 0.005 mol) in the same solvent (80 ml). The contents were refluxed on a steam-bath with TLC monitoring. After completion of the reaction (15 hr), ethanol was removed under reduced pressure and the product (**7a**) collected under

suction and recrystallised from ethanol, m.p. >300°; yield 62% (Found: C, 63.4; H, 3.2; N, 8.5. $C_{17}H_{10}N_2O_3S$ requires C, 63.3; H, 3.1; N, 8.7%); PMR: δ 7.46-7.86 (*m*, 7H, aromatic), 6.66 (*s*, 1H, $=\overset{|}{C}H$), 6.27 (*s*, 2H, $-OCH_2O-$).

Other *p*-substituted α-thiocyanoketones, viz. *p*-methyl-α-thiocyano acetophenone and *p*-chloro-α-thiocyano acetophenone were also condensed with **1a** under identical conditions to afford **7b** and **7c**, respectively which were recrystallised from ethanol. **7b**: m.p. >300°; yield 55% (Found: C, 64.5; H, 3.4; N, 8.5. $C_{18}H_{12}N_2O_3S$ requires C, 64.3; H, 3.6; N, 8.3%); PMR: δ 7.52-7.83 (*m*, 6H, aromatic), 6.71 (*s*, 1H, $=\overset{|}{C}H$), 6.23 (*s*, 2H, $-OCH_2O-$), 2.56 (*s*, 3H, $-C_6H_4.CH_3$). **7c**: m.p. >300°; yield 70% (Found: C, 57.0; H, 2.7; N, 7.5. $C_{17}H_9ClN_2O_3S$ requires C, 57.2; H, 2.5; N, 7.8%); PMR: δ 7.50-7.90 (*m*, 6H, aromatic), 6.76 (*s*, 1H, $=\overset{|}{C}H$), 6.24 (*s*, 2H, $-OCH_2O-$).

Methyl 6-aminopiperonylate hydrobromide (**1b**) was prepared as usual, m.p. 230°; yield 87%.

1,2-*Dihydro*-5*H*-1,3-*dioxolo*[4,5-*g*]*thiazolo*-[3,2-*a*]*quinazolin*-5-*one* (**16**) *via condensation of* **1b** *and* β-*bromoethyl thiocyanate* (**11**)

1b (1.38 g; 0.005 mol) and **11**[9] (0.83 g; 0.005 mol) were mixed in a dry test tube. The contents were heated in an oil-bath at 140-50° for 2 hr, cooled, triturated with dry ether (2 ml) and the solid obtained collected under suction. The solid was treated with 10% aq sodium carbonate, washed with water, and the product crystallised from ethanol-ethyl acetate, m.p. >300°; yield 56%; IR (in nujol): 1685, 1620, 1450, 1378, 1255, 1022, 915 and 895 cm^{-1}; PMR ($CDCl_3$ + TFA): δ 7.74 (*s*, 1H, C_6-H aromatic), 7.10 (*s*, 1H, C_{10}-H aromatic), 6.33 (*s*, 2H, $-OCH_2O-$), 5.06 (*t*, 2H, $-\overset{|}{N}-CH_2CH_2-$), 4.10 (*t*, 2H, $-H_2C-CH_2-S-$) (Found: C, 52.9; H, 3.4; N, 10.9. $C_{11}H_8N_2O_3S$ requires C, 53.2; H, 3.2; N, 11.3%).

Methyl 6-*thiocyanatoaminopiperonylate* (**9**)

To a solution of **1** (0.97 g, 0.005 mol) in ethanol (40 ml) was added conc. HCl (1 ml) and potassium sulphocyanide (0.48 g; 0.005 mol). The contents were refluxed on a steam-bath for 6 hr. After concentration, the separated product was filtered under suction, washed with water and crystallised from ethanol, m.p. 153-55°; yield 0.78 g (61%); IR (in nujol): 3460, 3350, 2032, 1698, 1615, 1590, 1460, 1378, 1305, 1125, 1040, 930 and 870 cm^{-1} (Found: C, 47.4; H, 3.8; N, 11.2. $C_{10}H_{10}N_2O_4S$ requires C, 47.2; H, 3.9; N, 11.0%).

Formation of **16** *via condensation of* **9** and 1,2-*dibromoethane* (**10**)

9 (0.25 g; 0.001 mol) and **10** (0.23 g; 0.0012 mol) were mixed in a dry test tube. The contents were heated on a water-bath for 30 min and then the temperature was raised to 140-50° for 2 hr. Heating was continued for another 30 min to ensure completion of reaction. It was cooled, triturated with dry ether (2 ml) and the solid obtained collected under suction. The product was treated with 10% aq sodium carbonate, washed with water and crystallised from ethaol-ethyl acetate, m.p. >300°; yield 0.15 g (62%).

In an another experiment, **9** (1 g) was taken in excess over **10** (10 ml) and heated on a water-bath for 30 min. After filtration, the residue was found to be **1b** by direct comparison (m.p., m.m.p., R_f and co-IR) with an authentic sample. The filtrate on fractional distillation gave unreacted **10** and **11** (ν_{max} 2160 cm^{-1}).

2-*Bromothiazoline hydrobromide* (**19**)

Dry hydrobromic acid gas was bubbled through a chilled etheral solution of **11** (4 g) for 30-55 min with continuous stirring. Ether was evaporated off and the residue crystallised from acetone-ether, m.p. 85°; yield 5.50 g; (92%) (Found: N, 5.9. $C_3H_5Br_2NS$ requires N, 5.7%).

Compound (**19**, 4 g) was basified with 10% aq sodium carbonate solution and extracted with (4 × 15 ml) ether. The ether extract was washed with water and dried (Na_2SO_4). Removal of solvent on a steam-bath gave the free base of **19** which was purified by fractional distillation and the fraction at 100-101°/12 mm was collected; yield 1.80 g (67%); PMR ($CDCl_3$): δ 3.73 (*t*, 2H, $=N-CH_2-CH_2-$), 3.43 (*t*, 2H, $-CH_2-CH_2-S-$) (Found: C, 21.3; H, 2.6; N, 8.6. C_3H_4BrNS requires C, 21.7; H, 2.4; N, 8.4%).

7,8-*Dihydro*-10*H*-1,3-*dioxolo*[4,5-*g*]*thiazolo*-[2,3-*b*]*quinazolin*-10-*one* (**17**)

A mixture of **19** (0.25 g; 0.001 mol), **1** (0.20 g; 0.001 mol) and phenol (4-5 drops) was heated in an oil-bath at 110-20° for 1 hr. The temperature was raised to 120-40° and the contents heated for another 3hr. It was cooled, washed with dry ether and the solid that separated out was collected under suction. The product was treated with dilute aq NaOH, washed with water and crystallised from ethanol, m.p. 205-6°; yield 0.12 g (48%); PMR ($CDCl_3$ + TFA): δ 7.83 (*s*, 1H, C_{11}-H aromatic), 7.16 (*s*, 1H, C_4-H aromatic), 6.45 (*s*, 2H, $-OCH_2O-$), 5.13 (*t*, 2H, $-\overset{|}{N}-CH_2-CH_2-$), 4.12 (*t*, 2H, $-CH_2-CH_2-S-$) (Found: C, 53.6; H, 3.4; N, 11.6. $C_{11}H_8N_2O_3S$ requires C, 53.2; H, 3.2; N, 11.3%).

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Synthesis of 9-Aryl- & 9-Hetaryl-5-(*p*-tolyl)-4,5,6,9-tetrahydrobenzo-[*de*]-*v*-triazolo[4,5-*g*]isoquinoline-4,6-diones & 4-(2*H*-Naphtho[1,2-*d*]-triazol-2-yl)-N-(*p*-tolyl)naphthalimides

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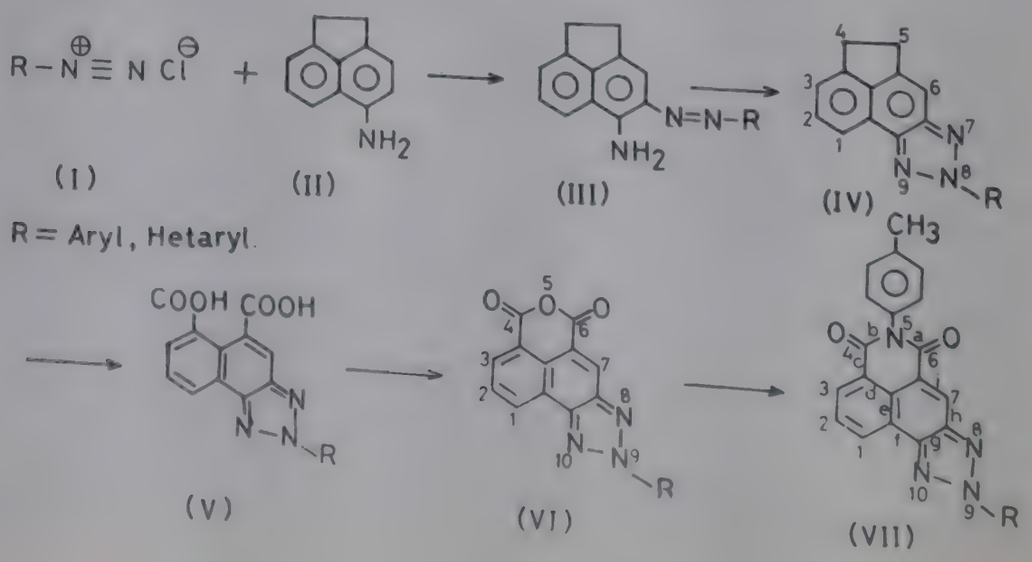
5-Amino-4-arylazo- and 5-amino-4-hetarylazo-acenaphthenes (III) have been prepared from aryl- and hetaryl- diazonium salts(I) by coupling with 5-aminoacenaphthene (obtained by nitration of acenaphthene and reduction) and triazolised using copper acetate in DMF in a current of air to give 8-aryl- and 8-hetaryl-8*H*-acenaphtho[4,5-*d*]triazoles(IV). These acenaphthotriazoles on oxidation to the corresponding 2H-naphtho[1,2-*d*]triazole-5,6-dicarboxylic acids(V) followed by cyclization to the corresponding anhydrides(VI) have been converted into 9-aryl- and 9-hetaryl-5-(*p*-tolyl)-4,5,6,9-tetrahydrobenzo[*de*]-*v*-triazolo[4,5-*g*]isoquinoline-4,6-diones(VII). 4-Amino-N-(*p*-tolyl)naphthalimide(VIII), prepared from acenaphthene by a series of reactions, is diazotised and coupled with suitable aminonaphthalenes to give the corresponding 4-(*o*-aminonaphthylazo)-N-(*p*-tolyl)naphthalimides(X,XI) which on triazolisation using copper acetate in DMF in a current of air give 4-(2*H*-naphtho[1,2-*d*]-triazol-2-yl)-N-(*p*-tolyl)naphthalimides(XII) with or without containing a sulphonic acid group in naphthalene part. The sulphonic acid derivative (XIIb), is converted into sulphonyl chloride and subsequently condensed with amines to give the sulphonamide derivatives(XIIc-f). The spectral characteristics of VII and XII have been studied.

4-Substituted derivatives of naphthalimide constitute a well known fluorophoric system which has been exploited in the preparation of valuable fluorescent compounds[1-3]. Recently there has been a trend to combine two or more different fluorophoric systems in appropriate manner to get compounds with improved fluorescent effects. In the present work, we have combined the two well known fluorophoric systems, naphthalimide and triazole to get compounds with good fluorescence. Since the substitution in 4-position of naphthalimide is expected to impart good fluorescent properties, it was envisaged to synthesise compounds in which either a triazole system is fused to naphthalimide in 3,4-positions or it is present as a substituent in 4-position.

The attempt to synthesise substituted 5-(*p*-tolyl)-4,5,6,9-tetrahydrobenzo[*de*]-*v*-triazolo[4,5-*g*]isoquinoline-4,6-diones(VII) by coupling suitable diazo components with 4-amino-N-(*p*-tolyl)naphthalimide and subsequent cyclization failed as the coupling was sluggish preventing the isolation of *o*-aminoazo compounds. Compounds VII were therefore prepared from substituted 8*H*-acenaphtho[4,5-*d*]triazoles (IV) which in turn were prepared from the diazotised aromatic and heterocyclic amines(I) by coupling reaction with 4-aminoacenaphthene(II) followed by triazolisation of the resulting *o*-aminoazo compounds(III). The conversion of IV into VII was effected by oxidation of IV with dichromate-acetic acid to substituted 2*H*-naphto[1,2-*d*]triazole-5,6-



(I) (II) (III) (IV) (V) (VI) (VII)

Table 1 – Characterization Data of 9-Aryl- and 9-Hetaryl-5-(*p*-tolyl)-4,5,6,9-tetrahydrobenzo[*de*]-*v*-triazolo[4,5-*g*]isoquinoline-4,6-diones(VII) and 4-(5-Substituted-2*H*-naphtho[1,2-*d*]triazol-2-yl)-N-(*p*-tolyl)naphthalimides(XII)

Compd*	R	Yield† (%)	m.p.‡ °C	Mol. formula
VIIa	*p*-Anisyl	42	>340	$C_{26}H_{18}N_4O_3$
VIIb	*p*-Toluyl	44	>340	$C_{26}H_{18}N_4O_2$
VIIc	1-Naphthyl	46	>340	$C_{29}H_{18}N_4O_2$
VIId	2-Thiazolyl	44	>340	$C_{22}H_{15}N_5O_2S$
VIIe	6-Methoxy-2-benzothiazolyl	50	>340	$C_{27}H_{17}N_5O_3S$
XIIa	H	87.4	297-98	$C_{29}H_{18}N_4O_2$
XIIb	SO_3H	89.1	δ	$C_{29}H_{18}N_4O_5S$
XIIc	SO_2NHCH_3	67.5	311	$C_{30}H_{21}N_5O_4S$
XIId	$-SO_2NH-C_6H_4-NO_2(p)$	61.2	340-42	$C_{35}H_{22}N_6O_6S$
XIIe	1-Piperidylsulphonyl	60.7	328	$C_{34}H_{27}N_5O_4S$
XIIf	Morpholinosulphonyl	63.5	322-23	$C_{33}H_{25}N_5O_5S$

* All the compounds gave satisfactory elemental analyses.
† Yields are based on 5-aminoacenaphthene in the case of VII and on *o*-aminoazo compounds in the case of XII.
‡ Melting points are uncorrected.
δ Melting occurs over a long range of temperature.

dicarboxylic acids (V) followed by treatment of V with acetic anhydride under reflux and subsequent condensation of the resultant cyclic anhydrides (VI) with *p*-Toluidine. The oxidation of IV to V was found to be facile and did not affect the triazole ring in agreement with the observation reported by Charrier and Baretta[4].

The aromatic and heterocyclic amino compounds used as diazo components in the present work were *p*-anisidine, *p*-toluidine, 1-naphthylamine, 2-aminothiazole and 2-amino-6-methoxybenzothiazole. The triazolisation of III was studied under different conditions. The best results were obtained by heating III with half a mol equiv. of cupric acetate in dimethylformamide at 80-90° under a current of air. Under these conditions triazolisation required a shorter reaction period and gave purer products in higher yields. The characterization data of VII are given in Table 1.

4-(5-Substituted-2*H*-naphtho[1,2-*d*]triazol-2-yl)-N-(*p*-tolyl)naphthalimides (XII) were synthesised using 4-amino-N-(*p*-tolyl)naphthalimide (VIII) as diazo component which was obtained through a sequence of reactions starting from acenaphthene[5]. Since 4-phenyltriazolyl derivatives of N-alkylnaphthalimides were tested as fluorescent compounds[6,7], it was also thought of interest to prepare 4-(5-sulphonamido-2*H*-naphtho[1,2-*d*]triazol-2-yl)-N-(*p*-tolyl)naphthalimides as fluorescent compounds. The compound VIII was diazotised with nitrosylsulphuric acid and the resultant diazonium salt (IX) coupled with 2-aminonaphthalene-1-sulphonic acid and 1-aminonaphthalene-4-sulphonic acid to get 4-(2′-amino-1′-naphthylazo)-N-(*p*-tolyl)naphthalimide(X) and 4-(1′-amino-4′-sulpho-2′-naphthylazo]-N-(*p*-tolyl)naphthalimide(XI), respectively. The compounds X and XI were triazolised to XIIa and XIIb respectively. The sulphonic acid group in XIIb was subsequently converted into sulphonyl chloride in chlorobenzene in the presence of dimethylformamide. The sulphonamide derivatives XIIc-f were prepared by treating the sulphonyl chloride with methylamine, *p*-nitroaniline, piperidine and morpholine respectively. The characterization data of XII are given in Table 1.

Both the series of naphthalimidotriazoles (VII and XII) exhibited a greenish-blue to blue fluorescence in day-light in dimethylformamide. Their fluorescent spectra were recorded and their spectral characteristics compared with those of the standard fluorescent compound 7-diethylamino-4-methylcoumarin (Table 2).

9-Aryl- and 9-hetaryl-5-(*p*-toluyl)-4,5,6,9-tetrahydrobenzo[*de*]-*v*-triazolo[4,5-*g*]isoquinoline-4,6-diones(VII) exhibited green to greenish-blue fluorescence in DMF. Their absorption maxima appeared in the range 358-388 nm and fluorescence emission maxima in the range 457-474 nm. The fluorescence intensity of these compounds was comparable with that of the standard. Among the compounds VII, 9-(2-thiazolyl)-5-(*p*-tolyl)-4,5,6,9-tetrahydrobenzo[*de*]-*v*-triazolo[4,5-*g*]isoquinoline-4,6-dione(VIId) exhibited the most intense fluorescence and the *p*-tolyl derivative (VIIe) the least intense fluorescence. Compounds XII exhibited an intense blue fluorescence in DMF. Their absorption maxima lay in the range 368-398 nm and the fluorescence emission maxima in the range 442-478 nm. The fluorescence intensity of

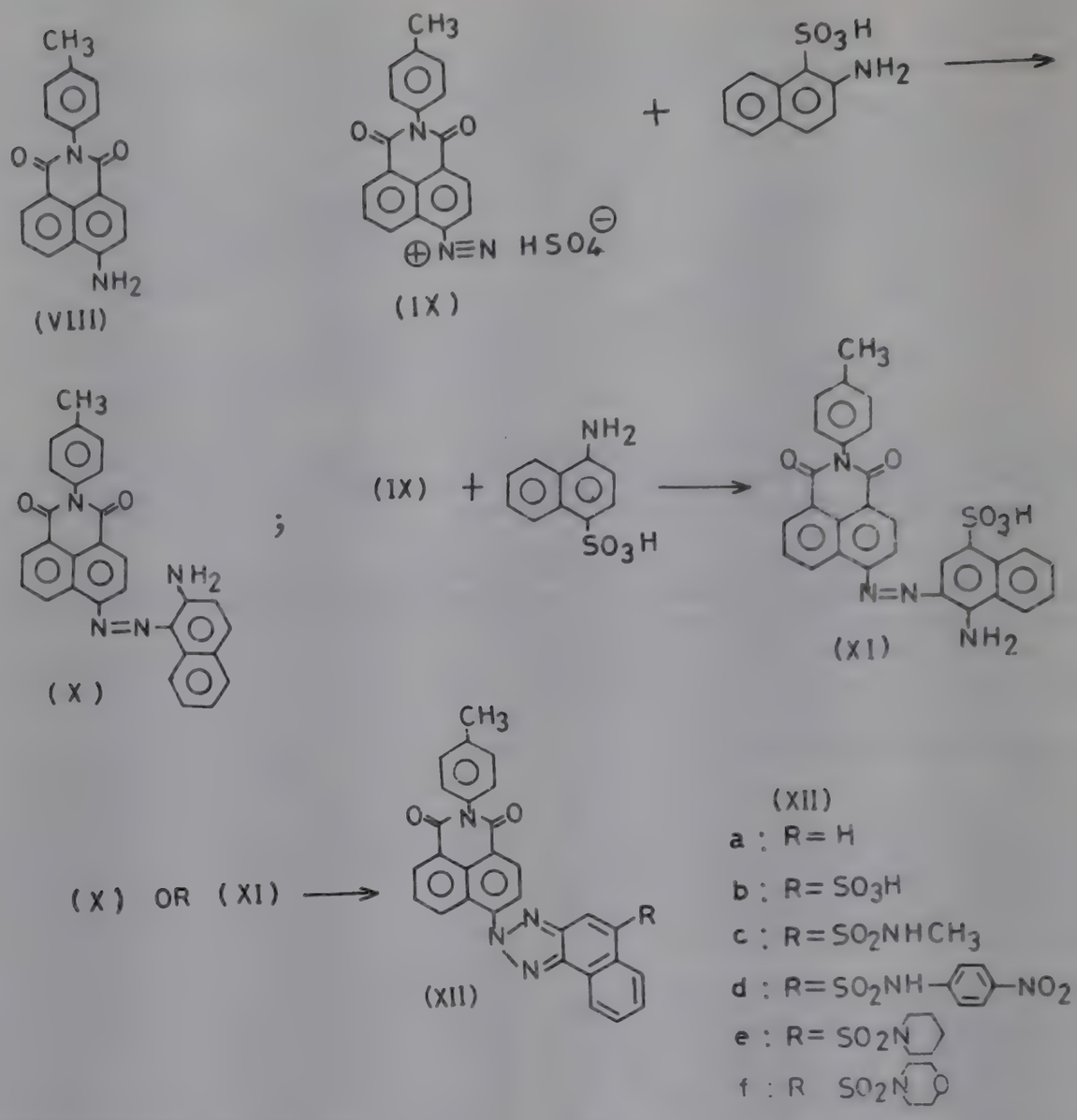


Table 2 — Spectral Characteristics of 9-Aryl- and 9-Hetaryl-5-(*p*-tolyl)-4,5,6,9-tetrahydrobenzo[*de*]-*v*-triazolo[4,5-*g*]-isoquinoline-4,6-diones(VII) and 4-(5-substituted-2*H*-naphtho[1,2-*d*]triazol-2-yl)-N-(*p*-tolyl)naphthalimides (XII)

Compd	A (nm)	$\varepsilon \times 10^{-4}$	logε	*F* (nm)	M (mg)
Standard*	376	2.554	4.41	458	1.523
VIIa	358	1.659	4.22	474	1.976
VIIb	362	1.494	4.17	472	2.834
VIIc	388	2.869	4.46	462	1.067
VIId	383	3.947	4.60	457	0.868
VIIe	378	2.634	4.42	468	1.713
XIIa	381	3.746	4.57	447	0.958
XIIb	368	1.835	4.26	454	2.138
XIIc	372	2.273	4.36	444	1.664
XIId	398	1.263	4.10	478	2.789
XIIe	384	2.687	4.43	450	1.324
XIIf	386	3.189	4.50	442	1.167

A = Absorption maxima
ε = Excitation wavelength used.
F = Fluorescence emission maxima.
M = Quantity of the fluorescent compound dissolved in 100 ml of the solvent to obtain 100 units of intensity
* = 7-Diethylamino-4-methylcoumarin.

these compounds was found to be comparable with that of the standard fluorescent compound. The unsubstituted naphthotriazole (XIIa) had maximum intensity of fluorescence among the series XII. The intensity in this case was found to be more than that of the standard. The *p*-nitrosulphonamido derivative(XIId) showed the least intensity of fluorescence. On the basis of the above studies, it can be concluded that the compounds of the series VII and XII may function as effective optical brighteners.

Experimental Procedure

5-Aminoacenaphthene(II) was prepared from acenaphthene by a known procedure. The aryl- and hetaryl-diazonium salts(I) on coupling with II gave 3-arylazo- and 3-hetarylazo-4-aminoacenaphthenes(III) in fairly good yields (72-80%). The triazolisation of III to 8-aryl- and 8-hetaryl-8H-acenaphtho[4,5-*d*]triazoles(IV) was carried out by a modified procedure using copper acetate in DMF under a current of air. 4-Amino-N-(*p*-tolyl)naphthalimide(VIII) was prepared from acenaphthene by known procedures.

Oxidation of III to 2-substituted 2H-naphtho-[1,2-d]triazole-5,6-dicarboxylic acids(V) and their cyclization to the corresponding anhydrides(VI)

To a solution of III (0.05 mol) in hot acetic acid (100 ml) was added sodium dichromate (63.4 g, 0.21 mol) during 3 hr at 70-80° under stirring. The mixture was slowly heated to reflux and the refluxing continued for 5-6 hr. Thereafter, it was diluted with hot water (240 ml), cooled, filtered and the solid washed with dil. hydrochloric acid, boiled with 5% sodium carbonate solution (80 ml) for 30-45 min and filtered. The filtrate was cooled, acidified with dil. hydrochloric acid and the precipitated solid filtered, washed with water and dried to get V.

The dry solid (V) was taken in acetic anhydride (100 ml) and heated to reflux, and the refluxing continued for 4-5 hr using Dean-Stark water separator. During this period 25-30 ml of water was collected. The solution was then cooled to afford crystals of VI.

9-Aryl- and 9-hetaryl-5-(p-tolyl)-4,5,6,9-tetrahydrobenzo[de]-v-triazolo[4,5-g]isoquinoline-4,6-diones(VII)

The cyclic anhydride VI (0.01 mol) was intimately mixed with *p*-toluidine (10.7 g, 0.1 mol) and the mixture heated on a steam-bath for 1.5-2.5 hr, and steam distilled to recover excess *p*-toluidine. The remaining solid was warmed with dil. hydrochloric acid (20 ml, 10%) and filtered. The solid obtained was crystallised from DMF to get pure VII (Table 1).

4-(Aminonaphthylazo)-N-(p-tolyl)naphthalimides(X and XI)

4-Amino-N-(*p*-toluyl)naphthalimide(VIII, 1.51 g, 0.005 mol) was diazotised by nitrosylsulphuric acid and the clear solution containing the diazonium salt IX slowly added to a cooled solution of 2-aminonaphthalene-1-sulphonic acid or 1-aminonaphthalene-4-sulphonic acid (0.005 mol) in water (10 ml), at 0-10°C. The *p*H of the mixture was adjusted to 6-6.5 by the addition of sodium carbonate. Thereafter, the reaction mixture was stirred further for 4-5 hr at 0-10°C. At the end of the coupling reaction, the mixture was neutralised, the precipitated *o*-aminoazo compound (X or XI) filtered, washed with water and dried.

4-(2H-Naphtho[1,2-d]triazol-2-yl-N-(p-tolyl)-naphthalimides(XIIa, b; Table 1)

The *o*-aminoazo compound X or XI (0.01 mol) was taken in DMF (15-25 ml), cupric acetate (1 g, slight excess over 0.005 mol) added to it and the mixture stirred on a water-bath. A current of air was passed continuously through the reaction mixture and the temperature raised to 90°. The oxidation is continued at this temperature until the *o*-aminoazo compound completely disappeared (about 45 min). The reaction mixture was cooled and poured slowly into ice-cold dil. hydrochloric acid (100 ml, 5%) under stirring. The precipitated solid was filtered, washed with water and crystallised from acetic acid (A pinch of zinc dust was added to acetic acid to get rid of the last traces of the *o*-aminoazo compound).

4-(5-Chlorosulphonyl-2H-naphtho[1,2-d]triazol-2-yl)-N-(p-tolyl)naphthalimide

4-(5-Sulpho-2*H*-naphtho[1,2-*d*]triazol-2-yl)-N-(*p*-tolyl)naphthalimide (XIIb, $R = SO_3H$) was added to chlorobenzene (35 ml), the mixture heated under stirring and 10 ml chlorobenzene distilled to remove the last traces of moisture. The reaction mixture was cooled to 30°, and thionyl chloride (1.785 g, 0.015 mol) added to it slowly followed by addition of DMF (0.365 g, 0.005 mol). The reaction mixture was slowly heated to 60°, stirred at this temperature for 1 hr and then at 95° for 2 hr. Thereafter, it was cooled, filtered and the solid obtained dried, washed with pet. ether and again dried. The acid chloride (yield 4.3 g, 78%) was used as such in the next step.

4-(5-Sulphonamido-2H-naphtho[1,2-d]triazol-2-yl)-N-(p-tolyl)naphthalimides (XIIc-f; Table 1)

The above sulphonyl chloride was taken in DMF (25 ml), the mixture stirred at room temperature and the appropriate amine (0.015 mol) added to it. The reaction mixture was stirred for 20-30 min at room temperature and then heated, if necessary, to 70° and kept at this temperature until the reaction was complete (30-40 min, checked by Beilsteins test). Thereafter, it was cooled and poured into cold acidified water. The sulphonamide derivative thus separated was crystallised from DMF.

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Condensed Heterocyclics: Part XXI—Synthesis & Substitution Reactions of 4-Aza-6-bromobenzo-2,1,3-selenadiazole

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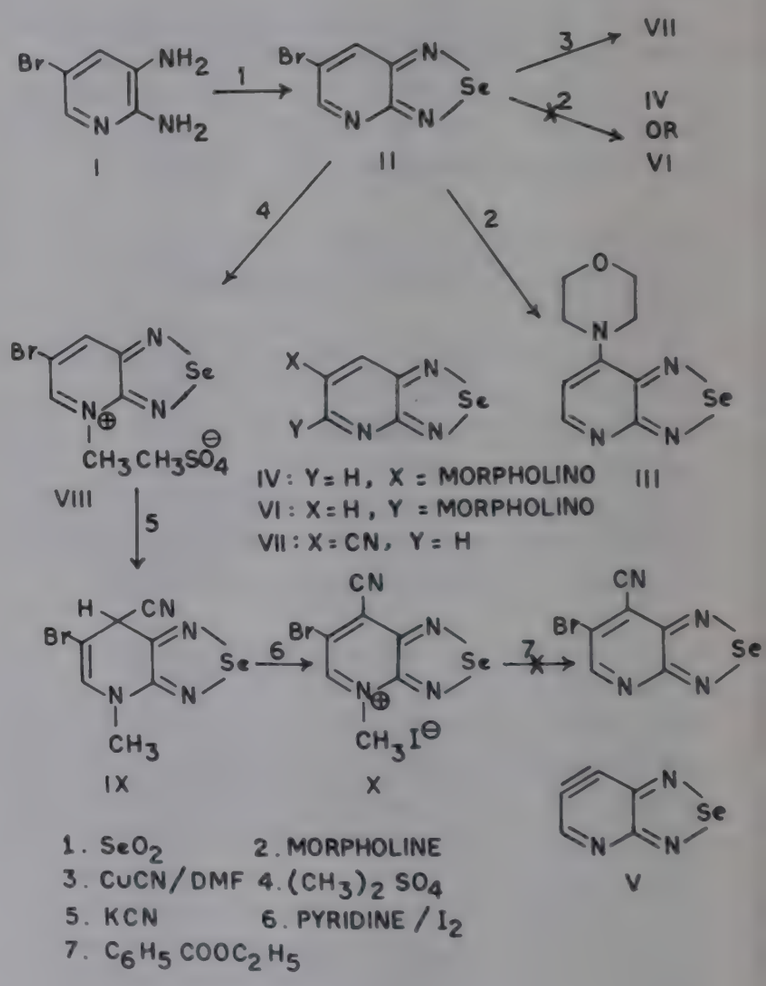
4-Aza-6-bromobenzo-2,1,3-selenadiazole(II) has been synthesised and its substitution reactions have been studied. Its reaction with morpholine gives 4-aza-7-N-morpholinobenzo-2,1,3-selenadiazole (III) via a benzyne mechanism.

4-Aza-6-bromobenzo-2,1,3-thiadiazole undergoes nucleophilic substitution with morpholine through a benzyne mechanism[1] leading to 4-aza-7-N-morpholinobenzo-2,1,3-thiadiazole, and a normal displacement reaction with cuprous cyanide. In view of these interesting reactions and in order to compare reactions of sulphur and selenium analogues, we report herein synthesis and substitution reactions of 4-aza-6-bromobenzo-2,1,3-selenadiazole.

5-Bromo-2,3-diaminopyridine (I)[2] on reaction with selenium dioxide in dioxane afforded 4-aza-6-bromobenzo-2,1,3-selenadiazole (II). Compound (II) when heated under reflux with morpholine gave exclusively 4-aza-7-N-morpholinobenzo-2,1,3-selenadiazole (III) with no trace of its 6-substituted isomer (IV) as revealed by its PMR spectrum (see Experimental). That the compound is a 7-substituted derivative (III) and not a 6-substituted derivative (IV) is proved by the fact that the coupling constant between H-5 and H-6 in the pyridine ring should be of the order of 2 Hz for structure (IV), instead of the observed 5.5 Hz. Same is true[3,4] for quinoline ring also.

The formation of 7-substituted product (III) could be explained by invoking a benzyne mechanism[1]. The hetryne would be formed by abstraction of a proton from the position-7 followed by formation of an additional bond between H-6 and H-7 leading to the proposed hetryne (V). The attack of morpholine on this hetryne then gives the 7-substituted derivative. The possibility of the compound being 5-substituted derivative (VI) has been ruled out by the fact that the coupling constant between H-6 and H-7 should be of the order of 8-9 Hz for structure (VI), thus unequivocally proving the structure of the compound as 4-aza-7-N-morpholinobenzo-2,1,3-selenadiazole (III).

The compound (II) on treatment with cuprous cyanide gave 4-aza-6-cyanobenzo-2,1,3-selenadiazole (VII) in 14.4% yield. The compound (II) on treatment with dimethyl sulphate afforded the methosulphate of 4-aza-6-bromobenzo-2,1,3-selenadiazole (VIII) and the latter on treatment with aqueous potassium cyanide afforded 4-aza-bromo-7-cyano-4,7-dihydro-N^4-methylbenzo-2,1,3-selenadiazole (IX) whose structure was corroborated by its PMR spectrum (see Experimental). IX underwent facile oxidation by iodine in pyridine to provide 4-aza-6-bromo-7-cyanobenzo-2,1,3-selenadiazole methiodide (X). However, when X was refluxed with ethyl benzoate a tarry mass was obtained, instead of the expected 4-aza-6-bromo-7-cyanobenzo-2,1,3-selenadiazole (XI).



Experimental Procedure

The melting points are uncorrected. The IR spectra were run on a Beckmann IR-20 and the PMR spectra on a Perkin-Elmer R-32 spectrometer.

4-*Aza*-6-*bromobenzo*-2,1,3-*selenadiazole* (*II*)

Selenium dioxide (1.05 g; 0.015 mol) was gradually added to a solution of diamine (I; 1.88 g; 0.01 mol) in dioxane (100 ml) and the reaction mixture refluxed for 6 hr, cooled, poured into cold water, the organic layer taken up in chloroform and aqueous layer extracted with chloroform. The combined chloroform extract was washed with water, dried (Na_2SO_4), solvent stripped off and residue purified by passing through a column of silica gel to procure II, 0.56 g (21.2%), m.p. 187-88° (Found: C, 22.7; H, 0.8; N, 15.9. $C_5H_2N_3SeBr$ requires C, 22.9; H, 0.8; N, 16.0%); IR(KBr): 3050 cm^{-1} (C−H of heterocyclics; PMR($CDCl_3$): δ 8.92 (1H, *d*, H-5), 8.40 (1H, *d*, H-7); $J_{5,7}=2.5$ Hz.

4-*Aza*-7-*N*-*morpholinobenzo*-2,1,3-*selenadiazole* (*III*)

4-Aza-6-bromobenzo-2,1,3-selenadiazole (II; 0.524 g; 0.002 mol) was taken in excess of dry morpholine (20 ml) and refluxed for 12 hr, poured into water (100 ml) and the organic material extracted with chloroform. The organic extract was washed with water, dried (Na_2SO_4), the solvent evaporated and the residue chromatographed to provide III, 0.14 g (26.1%), m.p. 161-62° (Found: C, 40.1; H, 3.8; N, 20.8. $C_{10}H_{10}N_4SeO$ requires C, 40.2; H, 3.7; N, 20.9%); PMR($CDCl_3$): δ 8.74 (1H, *d*, H-5), 6.39 (1H, *d*, H-6), 3.95 (8H, degenerate *t*, morpholino protons); $J_{5,6}=5.5$ Hz.

4-*Aza*-6-*cyanobenzo*-2,1,3-*selenadiazole* (*VII*)

To compound (II; 0.524 g; 0.002 mol) in dry DMF (15 ml) was added cuprous cyanide (0.358 g; 0.004 mol) and the reaction mixture was refluxed for 8 hr under exclusion of moisture. It was cooled, poured into water, the precipitates filtered off and stirred for 1 hr with a solution of potassium cyanide (5.0 g) in water (50 ml). The reaction mixture was extracted with chloroform and the combined chloroform extract was washed with water and dried (Na_2SO_4). Removal of the solvent and recrystallization from carbon tetrachloride provided VII, 0.06 g (14.4%) as light yellow-coloured crystals which shrank at 150° but did not melt upto 250° (Found: C, 34.5; H, 0.8; N, 26.1. $C_6H_2N_4Se$ requires C, 34.6; H, 1.0; N, 26.3%); IR(nujol): 2190 cm^{-1} ($\nu C\equiv N$).

Methosulphate of 4-*aza*-6-*bromobenzo*-2,1,3-*selenadiazole* (*VIII*)

Distilled and dried dimethyl sulphate (2.62 g; 0.02 mol) was added to a solution of II (1.34 g; 0.005 mol) in dry benzene (20 ml) and the reaction mixture refluxed for 8 hr under exclusion of moisture. The precipitated methosulphate was filtered, washed with benzene, dried *in vacuo* and crystallized from ethanol to obtain VIII, 1.30 g (67.0%), m.p. 238-39° (Found: C, 21.5; H, 2.0; N, 10.7. $C_7H_8N_3SSeO_4Br$ requires C, 21.6; H, 2.1; N, 10.8%).

4-*Aza*-6-*bromo*-7-*cyano*-4,7-*dihydro*-N^4-*methyl*-*benzo*-2,1,3-*selenadiazole* (*IX*)

To the methosulphate (VIII; 1.55 g; 0.004 mol) in water (20 ml) was gradually added with stirring potassium cyanide (2.5 g) in water (10 ml). The reaction mixture immediately turned greenish and the stirring was continued for 8 hr. The reaction mixture was extracted with chloroform, washed with water, dried ($MgSO_4$) and solvent evaporated to afford IX, 0.58 g (47.8%), m.p. 220-21° (Found: C, 27.5; H, 1.8; N, 18.8. $C_7H_5N_4SeBr$ requires C, 27.7; H, 1.7; N, 18.5%); IR(nujol): 2210 cm^{-1} ($\nu C\equiv N$); PMR($CDCl_3$/TFA): δ 8.65 (1H, *d*, H-5), 7.15 (1H, *d*, H-7) and 3.95 (3H, *s*, CH_3); $J_{5,7}=2.0$ Hz.

Methiodide (*X*) *of* 4-*aza*-6-*bromo*-7-*cyano*-*benzo*-2,1,3-*selenadiazole*

To IX (0.454 g; 0.0015 mol) taken in dry distilled pyridine (10 ml) was added iodine (0.25 g) in cold dry ethanol (10 ml) at 0° during 30 min, stirred at 0° for 8 hr and left in a refrigerator for 48 hr. Ethanol was evaporated on a water-bath and pyridine was removed under reduced pressure. The residue, thus left, was dissolved in hot water and filtered. The filtrate was concentrated (to 15 ml) and cooled in ice. The desired product (X) crystallized as bright yellow coloured solid (0.17 g; 26.8%), m.p. > 260° (Found: C, 19.4; H, 0.80; N, 12.8. $C_7H_4N_4SeBr$ I requires C, 19.6; H, 0.9 and N, 13.1%); IR(nujol): 2210 cm^{-1} ($\nu C\equiv N$).

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Some New Thiazole Derivatives from Dihydrochalcones

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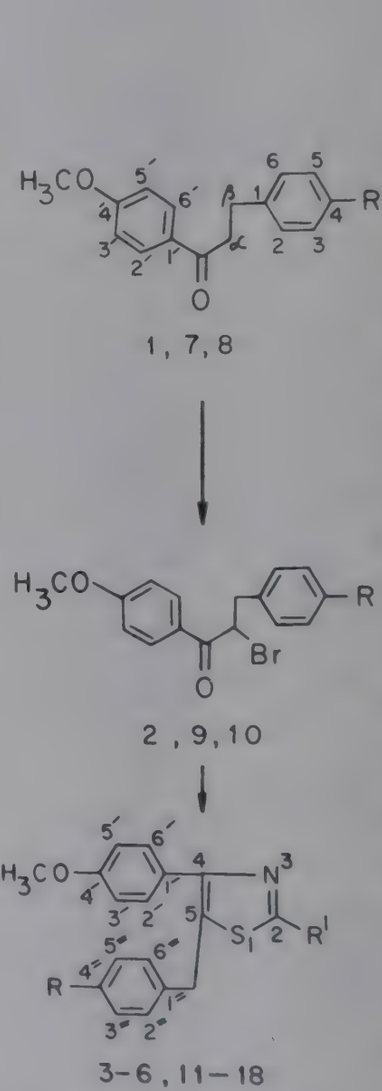
α-Bromo-α,β-dihydrochalcones on condensation with thiourea and ammonium dithiocarbamate afford 2-amino- and 2-mercapto-4-aryl-5-arylmethylthiazoles, respectively. The starting α-bromo derivatives are obtained by the bromination of corresponding dihydrochalcones.

Thiazoles are known to possess CNS stimulant[1], antitubercular[2,3], antibacterial[4,5], fungicidal[6-9], anthelmintic[10], hypotensive and hypothermic[11] activities. Thiazoles having 4-aryl-5-arylmethyl substituents do not appear to have been synthesised so far. Chalcones appear to be suitable starting materials towards such thiazoles. Earlier attempts to prepare these thiazoles from chalcones met with failure[12]. It was, therefore, considered of interest to develop a route to obtain these thiazoles using dihydrochalcones as starting materials.

As a test case α,β-dihydro-4'-methoxy-4-methylchalcone (**1**) on bromination with bromine in carbon tetrachloride gave a product which gave a positive DNP test. On the basis of its IR and PMR data (see Experimental) it could be assigned the structure as α-bromo-α,β-dihydro-4-methyl-4'-methoxychalcone (**2**). The chalcone (**2**) on condensation with thiourea in absolute ethanol afforded a yellow crystalline solid, containing both nitrogen and sulphur in its molecular framework. On the basis of its elemental analyses, IR and PMR data (see Experimental) it was assigned the structure as 2-amino-4-(4'-methoxyphenyl)-5-(4''-methylphenylmethyl)thiazole (**3**). The presence of amino group in **3** was further confirmed by the PMR spectral data of its acetate (**4**).

Chalcone (**2**) on condensation with ammonium dithiocarbamate in absolute ethanol afforded a colourless crystalline solid containing both nitrogen and sulphur in its molecular architecture. Finally its structure as 2-mercapto-4-(4'-methoxyphenyl)-5-(4''-methylphenylmethyl)thiazole (**5**) was settled by its IR and PMR data (see Experimental). The presence of mercapto group in **5** was further confirmed by the synthesis of its methyl derivative (**6**).

Similarly α,β-dihydro-4'-methoxychalcone (**7**) and α,β-dihydro-4,4'-dimethoxychalcone (**8**) on bromination gave α-bromo-derivatives (**9**) and (**10**) respectively. **9** on condensation with thiourea in absolute ethanol gave 2-amino-4-(4'-methoxyphenyl)-5-phenylmethylthiazole (**11**) as yellow shining needles,



which on acetylation afforded the corresponding 2-acetylamino derivative (**12**). **9** on condensation with ammonium dithiocarbamate afforded 2-mercapto-4-(4'-methoxyphenyl)-5-phenylmethylthiazole (**13**) as colourless shining needles. Methylation of **13** resulted in the corresponding 2-methylmercapto derivative (**14**).

Compound (**10**) on condensation with thiourea in absolute ethanol gave 2-amino-4-(4'-methoxyphenyl)-5-(4''-methoxyphenylmethyl)thiazole (**15**) as yellow flakes, which on acetylation furnished the correspond-

ing 2-acetylamino derivative (**16**). **10** on condensation with ammonium dithiocarbamate afforded 2-mercapto-4-(4′-methoxyphenyl)-5-(4″-methoxyphenyl methyl)thiazole (**17**) as colourless flakes. Methylation of **17** resulted in the corresponding 2-methylmercapto derivative (**18**).

Structures of all these compounds were assigned on the basis of elemental analyses and spectral data.

Biological activity

Compounds **3-6** and **11-18** were tested for their antifungal activity against two fungi *Aspergillus fumigatus* and *A. niger* at concentrations of 25 μg/ml and 50 μg/ml. Of these, **16** showed maximum inhibition against *A. niger* at 50 μg/ml, while **3**, **15** and **17** showed moderate activity. Rest of the compounds were devoid of any significant activity.

Compounds (**3-6**) and (**11-18**) were also tested for *in vitro* antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Compounds (**17**) and (**15**) showed marginal activity at 50 μg/ml against *Esch. coli* and *Staph. aureus* respectively. Other compounds displayed very weak antibacterial activity.

Experimental Procedure

α-Bromo-α,β-dihydro-4′-methoxy-4-methyl-chalcone (**2**): *Typical procedure*

Bromine (0.68 g as 10% solution in carbon tetrachloride) was added dropwise to a solution of the α,β-dihydro-4′-methoxy-4-methylchalcone (**1**; 1 g) with stirring at 30-35° during 40 min. The solvent was distilled off and the residue purified by passing through a column of silica gel and eluting it with benzene-pet. ether (1:19) when **2** was obtained as light yellow oil (1.25 g, 95%); PMR($CDCl_3$): δ 2.01 (*s*, 3H, CH_3), 3.21-3.56 (*m*, 2H, H-β), 3.73 (*s*, 3H, OCH_3), 5.20 (*t*, J=7 Hz, 1H, H-α), 6.77 (*d*, J=9 Hz, 2H, H-3′, H-5′), 7.03 (*s*, 4H, H-2, H-3, H-5, H-6), 7.85 (*d*, J=9 Hz, 2H, H-2′, H-6′).

2-Amino-4-(4′-methoxyphenyl)-5-(4″-methyl-phenylmethyl)thiazole (**3**):
Typical procedure

A solution of **2** (1 g) in absolute ethanol (25 ml) was refluxed for 4 hr with thiourea (0.26 g) and the solvent distilled off. The solid obtained after the addition of crushed ice and liquor ammonia was filtered, washed with water, dried and crystallised from benzene to give **3** as yellow shining prisms (0.8 g, 86%), m.p. 191-92°; PMR($CDCl_3$ + 1 drop of TFA): δ 2.59 (*s*, 3H, CH_3), 3.80 (*s*, 3H, OCH_3), 3.88 (*s*, 2H, CH_2), 6.97 (*d*, J=9 Hz, 2H, H-5′, H-3′), 7.05 (*bs*, 4H, H-2″, H-3″, H-5″, H-6″), 7.35 (*d*, J=9 Hz, 2H, H-2′, H-6′).

2-Acetylamino-4-(4′-methoxyphenyl)-5-(4″-methylphenylmethyl)thiazole (**4**):
Typical procedure

A solution of **3** (0.2 g) in dry benzene was refluxed for 5 hr with acetic anhydride (0.08 ml) and the solvent distilled off. The solid obtained after the addition of crushed ice was filtered, washed with water, dried and crystallised from benzene-pet. ether to give **4** as light yellow shining needles (0.2 g, 88%); m.p. 145-46°; PMR($CDCl_3$): δ 1.55 (*s*, 3H, $COCH_3$), 2.31 (*s*, 3H, CH_3), 3.80 (*s*, 3H, OCH_3), 4.11 (*s*, 2H, CH_2), 6.88 (*d*, J =9 Hz, 2H, H-3′, H-5′), 7.04 (*bs*, 4H, H-2″, H-3″, H-5″, H-6″), 7.86 (*d*, J=9 Hz, 2H, H-2′, H-6′).

2-Mercapto-4-(4′-methoxyphenyl)-5-(4″-methyl-phenylmethyl)thiazole (**5**):
Typical procedure

Ammonium dithiocarbamate (0.37 g) was added to a solution of **2** (1 g) in absolute ethanol (25 ml) with stirring, the mixture refluxed for 1 hr and the solvent distilled off. The residue obtained was refluxed with benzene (10 ml), filtered and the filtrate cooled to afford **5** as colourless shining needles (0.83 g, 84%); m.p. 181-82°; PMR($CDCl_3$): δ 1.70 (*s*, 1H, SH, exchangeable with D_2O), 2.36 (*s*, 3H, CH_3), 3.86 (*s*, 3H, OCH_3), 3.92 (*s*, 2H, CH_2), 6.99 (*d*, J=9 Hz, 2H, H-3′, H-5′), 7.06-7.28 (*m* 4H, H-2″, H-3″, H-5″, H-6″), 7.36 (*d*, J=9 Hz, 2H, H-2′, H-6′).

2-Methylmercapto-4-(4′-methoxyphenyl)-5-(4″-methylphenylmethyl)thiazole (**6**):
Typical procedure

Dimethyl sulphate (0.09 ml) was added dropwise to a solution of **5** (0.2 g) in sodium hydroxide solution (10% aqueous, 10 ml), with stirring at 0-5°. Stirring was continued for further 20 min, the mixture extracted with ether (10 ml), the ether layer washed successfully with aq 10% sodium hydroxide, water and dried (Na_2SO_4). The solvent on distillation gave an oil, which was purified by passing through a column of silica gel and eluting it with benzene-pet. ether to give **6**

Table 1—Percentage Yields and Melting Points of Compounds (**9-18**)

Compd*	Yield (%)	m.p.† (°C)	Compd*	Yield (%)	m.p.† (°C)
9	94	oil	**10**	96	oil
11	86	155-56	**15**	85	174-76
12	88	134-36	**16**	88	171-72
13	85	180-81	**17**	81	141-42
14	76	oil	**18**	76	oil

*All the compounds gave satisfactory C, H analyses and their spectral data (IR, PMR) were compatible with the structures assigned.
†not corrected

as light yellow oil (0.17 g, 81%); PMR($CDCl_3$): δ 2.29 (*s*, 3H, CH_3), 2.59 (*s*, 3H, SCH_3), 3.76 (*s*, 3H, OCH_3), 4.09 (*s*, 2H, CH_2), 6.84 (*d*, $J=9$ Hz, 2H, H-3′, H-5′), 7.01 (*s*, 4H, H-2″, H-3″, H-5″, H-6″), 7.45 (*d*, $J=9$ Hz, 2H, H-2′, H-6′).

Some other compounds prepared by the typical procedures given above are listed in Table 1.

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Synthesis of Tetrahydrofuran Derivatives via Reaction of Iodine Azide with Oxygenated Olefinic Acids

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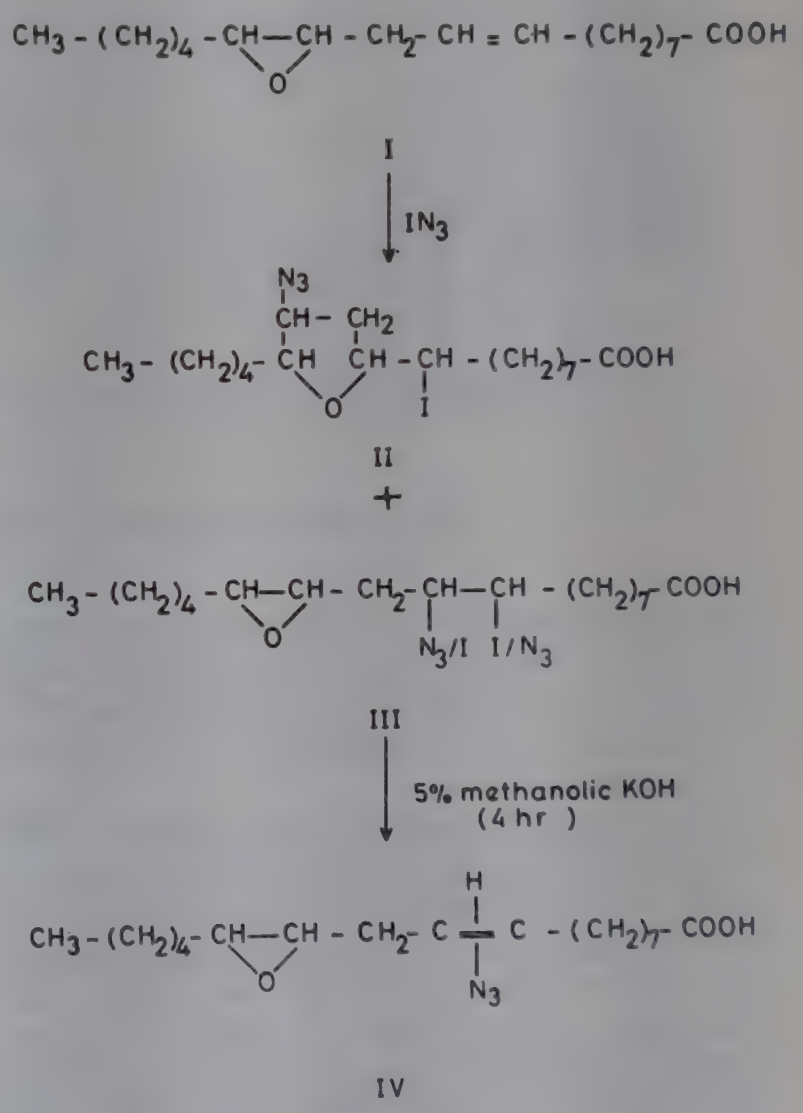
Vernolic acid (I) on treatment with iodine azide (IN_3) affords 12-azido-10, 13-epoxy-9-iodooctadecanoic acid (II) and *threo*-10(9)-azido-*cis*-12, 13-epoxy-9(10)-iodooctadecanoic acid (III). A similar reaction of *threo*-12(13)-chloro-13(12)-hydroxy-*cis*-9-octadecenoic acid (V) furnishes 12-chloro-10, 13-epoxy-9-iodooctadecanoic acid (VI) and *threo*-10(9)-azido-12(13)-chloro-13(12)-hydroxy-9(10)-iodooctadecanoic acid (VII). The iodazide adducts III and VII on reaction with methanolic KOH yield 9(10)-azido-*cis*-12, 13-epoxy-*trans*-9-octadecenoic acid (IV). The structures of the products have been established on the basis of their elemental analysis and IR, PMR and mass spectral data.

Organic and inorganic azides are excellent reagents used in the synthesis of a variety of compounds[1-3]. In continuation of our work[4,5] on the synthesis of tetrahydrofuran derivatives of potential physiological interest, we report in this paper the results of our investigation on the reaction of iodine azide (IN_3) with a β-epoxyolefinic acid (vernolic acid) and its chlorohydrin derivative. The aim of the present investigation is also to study the effect of neighbouring oxygenated group on the product composition. The reaction of this pseudohalogen (IN_3) with a variety of other olefinic acids have been reported earlier[6,7].

The β-epoxyolefinic acid (I; *cis*-12, 13-epoxy-*cis*-9-octadecenoic acid) on reaction with IN_3 gave two products, II and III (Scheme 1), which were separated by column chromatography.

Product II gave positive tests for iodine and nitrogen and analysed for $C_{18}H_{32}O_3N_3I$. Its IR spectrum exhibited characteristic bands at 2100, 1110, 1050 and 760 cm^{-1} due to azide, ether (C–O–C) and iodide functions respectively. The PMR spectrum displayed signals at δ 4.08 (*m*, –CH–I), 3.8 (*m*, 2H, –CH–O–CH–), 3.7 (*m*, 1H, –CH–N_3) and 1.9 (*m*, 2H, CH_2 of 1,4-epoxy ring). A part of the multiplet for CH–O–CH was merged into the multiplet observed for CH–N_3. On the basis of these data it was formulated as 12-azido-10, 13-epoxy-9-iodooctadecanoic acid (II). This structure was further supported by the mass spectral study (Fig. 1). The peaks at *m/z* 394 and 182 confirmed the position of 1,4-epoxide ring at C_{10}-C_{13}, and the ion peak at *m/z* 283 established the position of iodo function at C-9. Product II may be considered as a mixture of *cis*- and *trans*-distereoisomers, as observed by others[8] in similar type of reactions.

The isomeric product III, which also analysed for $C_{18}H_{32}O_3N_3I$ and gave positive tests for iodine and nitrogen, showed in its IR spectrum characteristic bands at 2100 (N_3), 840, 820 (epoxide) and a sharp band at 760 cm^{-1} (C–I). Its PMR spectrum displayed signals at δ 3.88 (*m*, 1H, –CH–I), 3.7 (*m*, 1H, –CH–N_3) and 2.9 (*m*, 2H, epoxide methines). The formation of this product was further supported by its mass spectrum fragmentation pattern (Fig. 2). On the



SCHEME 1

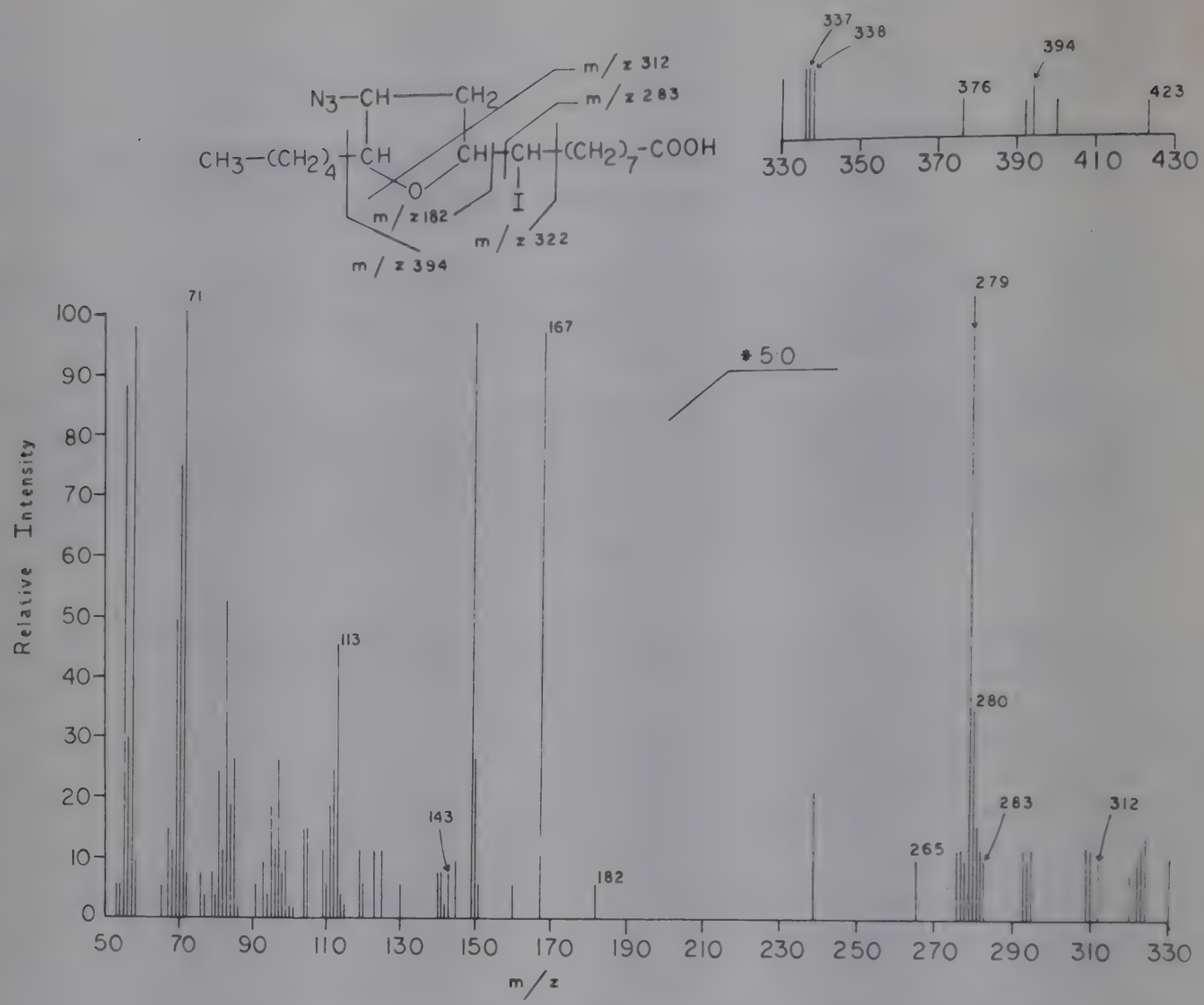


Fig. 1—Mass fragmentation of 12-azido-10,13-epoxy-9-iodooctadecanoic acid (II)

basis of these results III was formulated as *threo*-10(9)-azido-*cis*-12, 13-epoxy-9(10)-iodooctadecanoic acid. Addition of IN_3 to a double bond is stereospecific[9]: *cis*-olefins give *threo*-adducts while *trans*-olefins give *erythro*-adducts.

The iodoazide adduct III on treatment with methanolic KOH underwent dehydrohalogenation to give IV as the major product which was characterized as 9(10)-azido-*cis*-12, 13-epoxy-*trans*-9-octadecenoic acid (IV) on the basis of spectral studies. The elimination of HI is mostly regiospecific and give generally *trans*-vinyl azide derivative from *threo*-adduct rather than allyl azide[9]. The product (IV) analysed for $C_{18}H_{31}O_3N_3$ and did not respond to Beilstein test but gave unsaturation test. Its IR spectrum exhibited a strong and sharp band due to azide function at 2100 cm^{-1}. However, a new band at 1640 cm^{-1} was attributed to the stretching vibration of the carbon-carbon double bond in conjugation with the azide function. The absorption bands at 840 and 820 cm^{-1} were attributed to the epoxide ring. The PMR spectrum of this vinyl azide exhibited signals at δ 5.5 (*m*, 1H, $-CH=\overset{\cdot}{C}-$), 2.95 (*m*, 2H, oxirane methines) and 2.22 (*m*, 6H, $-CH_2-CH=C-CH_2$ and $-CH_2-COOH$).

Chlorohydrin V [*threo*-12(13)-chloro-13(12)-hydroxy-*cis*-9-octadecenoic acid] on a similar treatment with IN_3 gave a polar (VI) and a non-polar (VII) products (Scheme 2).

Product VI analysed for $C_{18}H_{32}O_3ClI$ and showed no azide band in its IR spectrum. Its PMR spectrum exhibited characteristic signals at δ 4.1 (br *m*, 2H, CH $-$Cl and CH $-$ I), 3.8 (*m*, 2H, $-CH-O-CH$) and 1.8 (*m*, 2H, $-CH_2$ of 1,4-epoxy ring). Thus, on the basis of these results it was formulated as 12-chloro-10, 13-epoxy-9-iodooctadecanoic acid. This product is also expected to be a mixture of *cis*- and *trans*-diastereomers on similar grounds as reported earlier[8].

The nonpolar product appeared to be the simple isomeric addition product on the basis of elemental

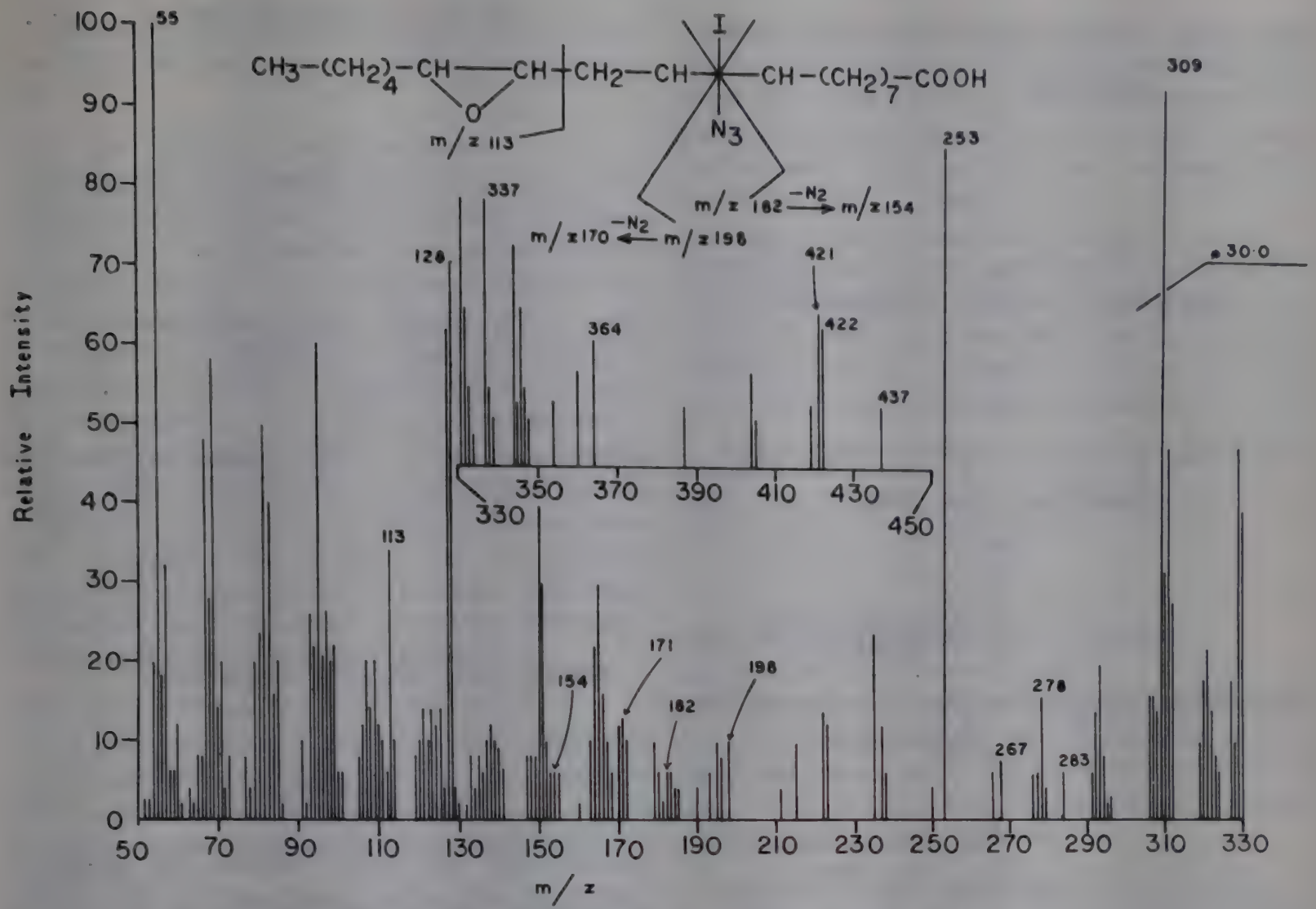


Fig. 1 —Mass fragmentation of *threo*-10(9)-azido-*cis*-12,13-epoxy-9(10)-iodooctadecanoic acid (III)

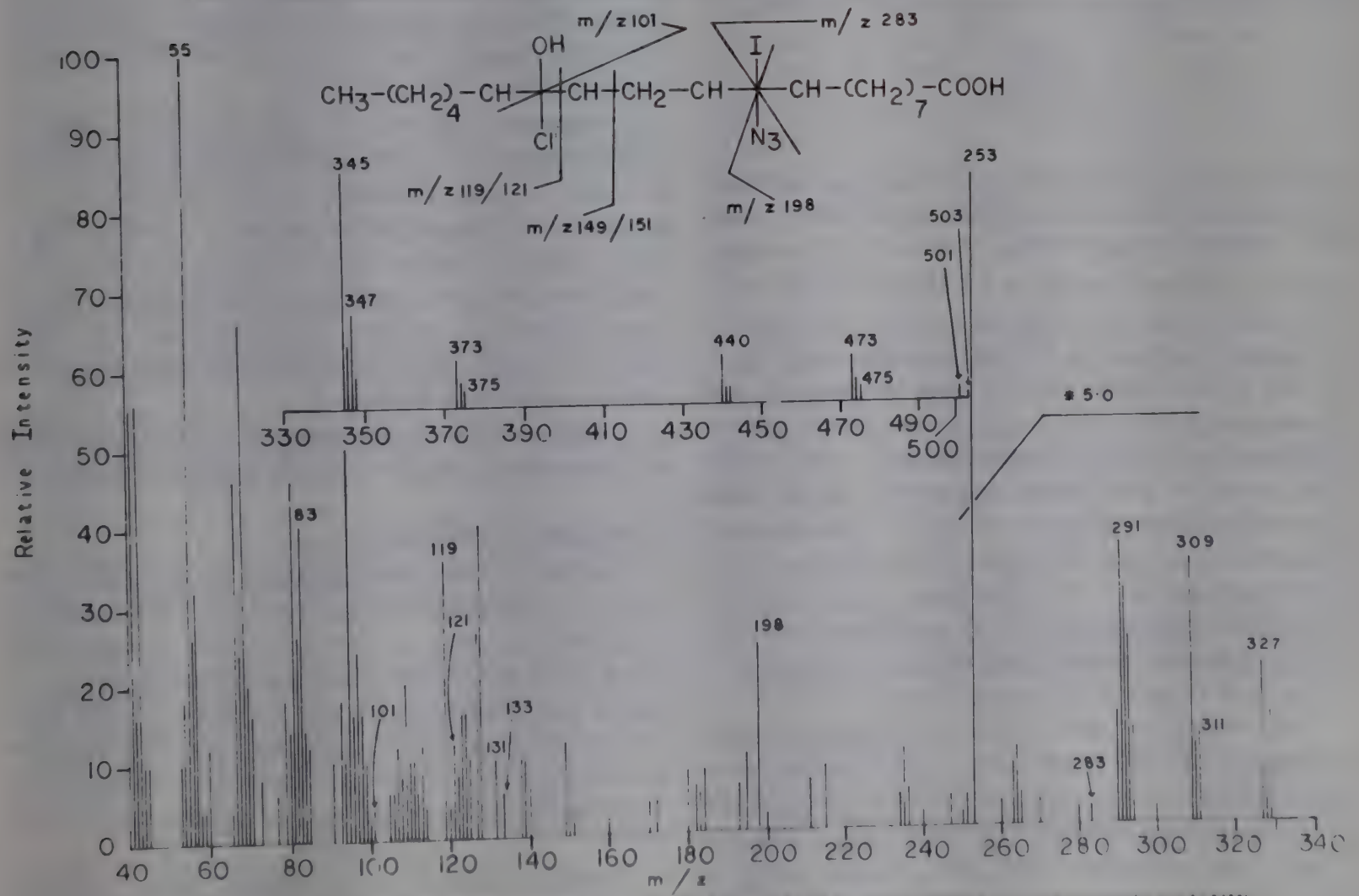
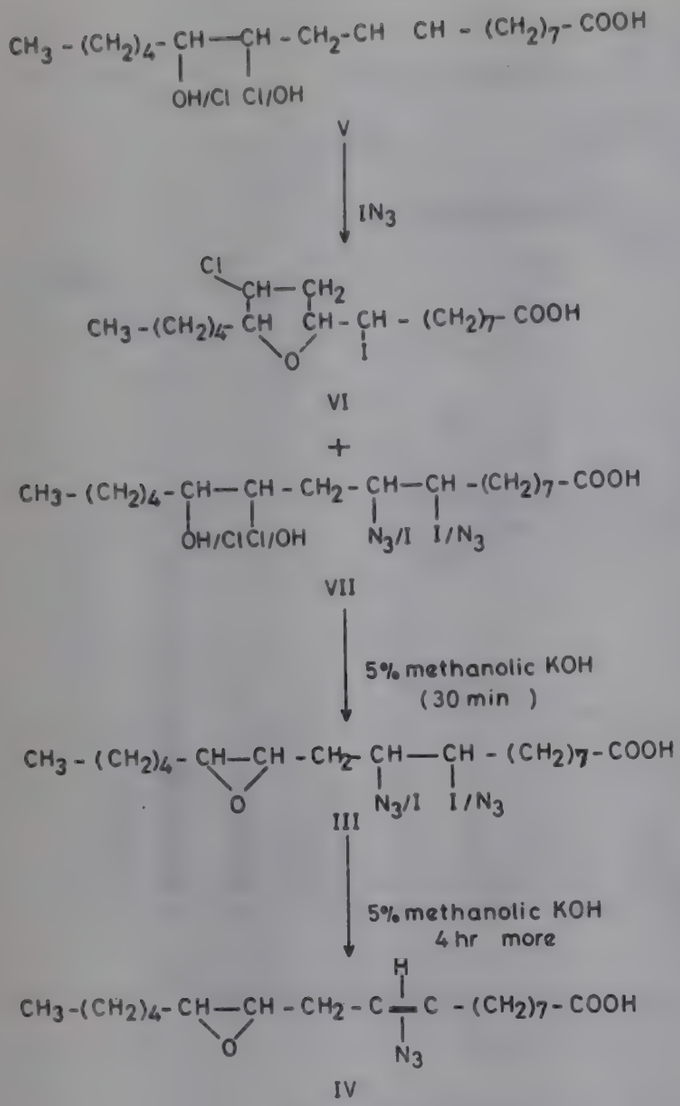
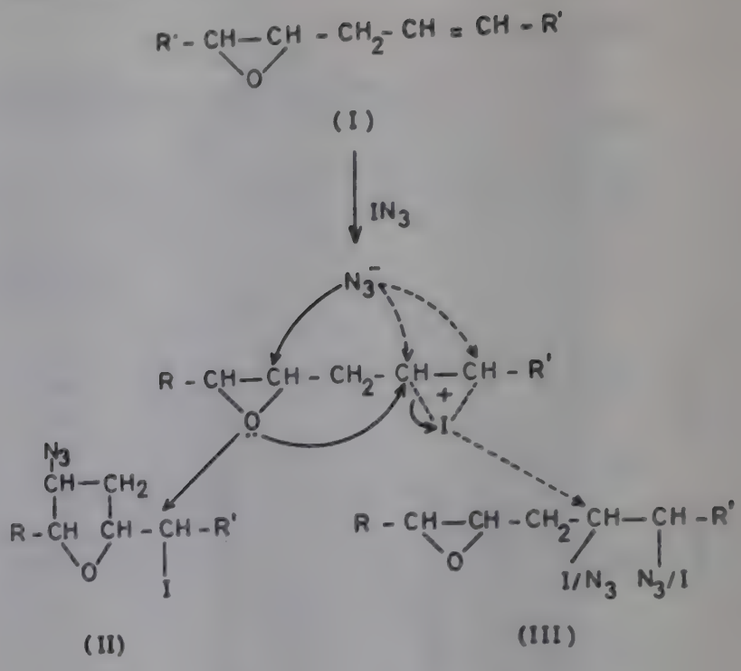


Fig. 3 —Mass fragmentation of *threo*-10(9)-azido-12(13)-chloro-13(12)-hydroxy-9(10)-iodooctadecanoic acid (VII)



SCHEME 2



Where R = $CH_3-(CH_2)_4$; R' = $(CH_2)_7-COOH$.

SCHEME 3

analysis ($C_{18}H_{33}O_3N_3ClI$). Its IR spectrum exhibited characteristic bands at 3500 (OH and CO*OH*), 2110 (N_3), 750 (C–I) and 720 cm^{-1} (C–Cl). The PMR spectrum displayed signals at δ 4.15 (*m*, 1H, CH–Cl), 3.88 (*m*, 1H, CH–I), 3.6 (*m*, 2H, –C*H*–OH and CH–N_3) and 3.0 (br, *s*, 1H, OH, exchangeable with D_2O). On the basis of these spectral data the product was characterized as *threo*-10(9)-azido-12(13)-chloro-13(12)-hydroxy-9(10)-iodooctadecanoic acid (VII). This structure was further supported by its mass spectral fragmentation pattern (Fig. 3). Appearance of a fragment ion at *m/z* 101 suggested the presence of the hydroxy group at C-13. The peak at *m/z* 119/121 showed the chloro group at C-13, and those at *m/z* 283 and 198 indicated the iodo and azido functions at C-9. These data suggest the isomeric nature of VII.

The iodoazide adduct VII on treatment with methanolic KOH underwent cyclodehydrochlorination to give a major product which was purified and characterized as *threo*-10(9)-azido-*cis*-12, 13-epoxy-9(10)-iodooctadecanoic acid (III) on the basis of spectral data identical with those given above. This product (III) was further treated with methanolic KOH for 4 hr. After usual work-up the reaction product which showed a dense spot along with other minor ones, was characterized as 9(10)-azido-*cis*-12, 13-epoxy-*trans*-9-octadecenoic acid exhibiting similar spectral data as that of IV.

Compounds III and VII are the simple iodazide addition products to the double bond, while products II and VI are expected to be formed by the neighbouring group participation of epoxide ring in the reaction occurring at the double bond. Neighbouring group participation of epoxide has also been observed earlier by Canonica *et al.*[10]. Mechanistically the formation of these products can be shown as given in Scheme 3.

In chlorohydrin V, the hydroxy group at γ-position acts in a similar way to form the cyclic compound VI.

Experimental Procedure

IR (neat) spectra were recorded on a Perkin Elmer 621 spectrophotometer (ν_{max} in cm^{-1}), PMR spectra in $CDCl_3/CCl_4$ on a Varian A60 spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a JEOL D-300 mass spectrometer. Silica gel was used for TLC analysis employing a 20% solution of perchloric acid as spray reagent. Pet. ether refers to the fraction with b.p. 40-60°.

Vernolic acid (I) was isolated from *Vernonia anthelmintica* seed oil by selective hydrolysis as

adopted earlier[5]. Its chlorohydrin derivative (V) was prepared by the reaction with trimethylchlorosilane in ether[11].

Iodine azide addition: General procedure

Vernolic acid (I) and its chlorhydrin (V) were treated with iodine azide according to the procedure of Fowler *et al.*[12]. To a stirred slurry sodium azide (7.5 g) in acetonitrile (50 ml) in an ice-bath was added slowly iodine monochloride (9.5 g) during 10-20 min. Thereafter the mixture was stirred for 5-10 min and the compound I or V added to it. The reaction mixture was allowed to attain the room temperature and stirred for 8-10 hr. In each case a red brown slurry was obtained which was poured into water (250 ml) and the mixture extracted thrice with ether (3 × 200 ml). These extracts were combined and washed with 5% sodium thiosulphate solution (150 ml) leaving a colourless ethereal solution. The solution was washed with water (900 ml) and dried over sodium sulphate.

Reaction of iodine azide with vernolic acid (I)

The β-epoxyolefinic acid (I) (1 g, 3.37 mmol) was treated with IN_3 according to the above procedure. The reaction mixture showed the formation of two products which were separated in pure state by column chromatography.

Elution with pet. ether-ether (92:8, v/v) gave the product II as a viscous dark brown liquid (~48%); gave positive Beilstein and nitrogen tests (Found: C, 46.5; H, 6.9; N, 9.0. $C_{18}H_{32}O_3N_3I$ requires C, 46.5; H, 6.9; N, 9.0%); IR: 3400 (carboxylic OH), 2100 (N_3), 1710 (carboxylic CO), 1110, 1050 (ether C–O–C) and 760 (C–I); PMR (CCl_4); 10.55 (*s*, 1H, COOH), 4.08 (*m*, 1H, CH–I), 3.8 (*m*, 2H, CH–O–CH), 3.7 (*m*, 1H, CH–N_3), 2.3 (*m*, 2H, CH_2–COOH), 1.9 (*m*, 2H, $-CH_2$ of 1,4-epoxy ring), 1.3 (br *s*, 2OH chain methylenes) and 0.9 (*t* like, 3H, $-CH_3$); MS: (*m/z*) 423 ($M-N_3$), 71 (base peak), molecular ion was absent.

Subsequent elution with pet. ether-ether (85:15, v/v) yielded the product III (~35%) which gave positive picric acid, Beilstein and nitrogen tests indicating the presence of epoxy function, halogen and nitrogen (Found: C, 46.5; H, 7.0; N, 9.1. $C_{18}H_{32}O_3N_3I$ requires C, 46.5; H, 6.9; N, 9.0%); IR: 3400 (carboxylic OH), 2100 (N_3), 1710 (carboxylic CO), 840, 820 (epoxy) and 760 (C–I); PMR (CCl_4): 10.64 (*s*, 1H, COOH), 3.88 (*m*, 1H, CH–I), 3.7 (*m*, 1H, CH–N_3), 2.9 (*m*, 2H, epoxide methines), 2.25 (*m*, 2H, $-CH_2$–COOH), 1.32 (br *s*, 2 2H chain methylenes), 0.9 (*t* like, 3H, $-CH_3$); MS: (*m/z*): 437 ($M-N_2$), 55 (base peak), molecular ion was absent.

Dehydroiodination of III: Formation of 9(10)-azido-cis-12,13-epoxy-trans-9-octadecenoic acid (IV)

The iodoazide adduct III (0.36 g) was stirred with KOH (0.72 g) in methanol (15 ml) for 4 hr, the reaction mixture acidified with 20% HCl and worked-up with ether. The ethereal layer was washed several times with water, dried, ether removed under reduced pressure and the residue subjected to column chromatography over silica gel.

Elution with pet. ether-ether (83:17, v/v) yielded IV (~0.18 g) as the major product (Found: C, 64.1; H, 9.3; N, 12.5. $C_{18}H_{31}O_3N_3$ requires C, 64.1; H, 9.3; N, 12.5%); IR: 2100 (N_3), 1640 (C=C), 840, 820 (epoxide); PMR (CCl_4): 10.1 (*s*, 1H, COOH), 5.5 (*m*, 1H, $-CH(N_3)-C=$), 2.95 (*m*, 2H, epoxide methines and 2.22 (*m*, 6H, $-CH_2-CH=C(N_3)-CH_2$ and CH_2COOH).

Reaction of iodine azide with 12(13)-chloro-13(12)-hydroxyoctadecenoic acid (V)

The reaction of iodine azide with chlorohydrin (V) (1 g, 3.01 mmol), carried out in the same way as described above, gave a mixture of two products (VI and VII) which were separated by column chromatography over silica gel.

Elution with pet, ether-ether (95:5, v/v) gave VI (~32%) as a thick brown liquid which responded positively to Beilstein test and negative to nitrogen test. (Found :C, 47.2; H, 7.3. $C_{18}H_{32}O_3ClI$ requires C, 47.1; H, 7.0%); IR: 3400 (carboxylic OH), 1710 (carboxylic CO), 1110, 1050 (C–O–C) and 755 (C–I and C–Cl); PMR ($CDCl_3$); 10.62 (*s*, 1H, COOH), 4.1 (br *m*, 2H, CH–Cl and CH–I), 3.8 (*m*, 2H, CH–O–CH), 2.3 (*m*, 2H, $-CH_2$–COOH), 1.8 (*m*, 2H, CH_2 of 1,4-epoxy ring), 1.3 (br *s*, 2OH chain methylenes), 0.88 (*t* like, 3H, $-CH_3$).

Subsequent elution with pet. ether-ether (90:10, v/v) yielded VII (~46%) which gave positive Beilstein and nitrogen tests (Found: C, 43.1; H, 6.6; N, 8.4. $C_{18}H_{33}O_3N_3ClI$ requires C, 43.1; H, 6.6; N, 8.4%); IR: 3500 (OH), 2110 (N_3), 1710 (carboxylic CO) and 750 (C–I), 720 (C–Cl); PMR ($CDCl_3$): 10.1 (*s*, 1H, COOH), 4.15 (*m*, 1H, –CH–Cl), 3.38 (*m*, 1H, –CH–I), 3.6 (*m*, 2H, –CH–N_3, –CH–OH), 3.0 (br *s*, 1H, OH, exchangeable with D_2O), 2.3 (*m*, 2H, $-CH_2COOH$), 1.35 (br *s*, 22H chain methylenes) and 0.9 (*t* like, 3H, $-CH_3$); MS: (*m/z*) 501/503 (M^+), 55 (base peak).

Dehydroiodination of VII

Dehydroiodination of VII (0.4 g) was carried out in the same manner as described above. Just after 30 min the formation of a product was detected, which was characterized as *threo*-10(9)-azido-*cis*-12, 13-epoxy-9(10)-iodooctadecanoic acid (III). It was obtained by

column chromatography using pet. ether-ether (92:8, v/v) as eluent yield ~0.36 g (90%); responded positively to picric acid (on TLC), nitrogen and Beilstein tests. Its IR and PMR spectra were similar to those of III obtained earlier (*vide supra*).

Product III was further treated with methanolic KOH for 4 hr. After usual work-up, the reaction product on TLC showed a dark spot with some minor ones. The major product after purification by column chromatography ~0.32 g was characterized as 9(10)-azido-*cis*-12, 13-epoxy-*trans*-9-octadecenoic acid (IV).

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Synthesis & QSAR Study of Some Newer 3-Mercapto/Alkylmercapto-5-(2′-methyl-6′-substituted quinolin-4′-yloxymethyl-4-(*p*-substituted phenyl)-4*H*-1,2,4-triazoles as Potent Antimalarials

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Some new 3-mercapto/alkylmercapto-5-(2′-methyl-6′-substituted quinolin-4′-yloxymethyl)-4-(*p*-substituted phenyl)-4*H*-1,2,4-triazoles have been synthesised by esterification of 4-hydroxy-2-methylquinolines (**1a,b**) followed by hydrazinolysis to give the acid hydrazides (**2a,b**). The latter products on condensation with aryl isothiocyanates followed by cyclization with NaOH furnish the title compounds which have been evaluated for their antimalarial activity. Quantitative structure activity relationship has also been studied. It has been observed that the best correlationship is described by the linear relationship of lipophilicity (log *P*) of the compounds with biological activity.

Quinoline derivatives occupy an important place as antimalarial agents[1-4], and constitute some of the best tolerated antimalarial drugs known so far. In continuation of our work on the synthesis of quinolines[5] it was thought judicious to prepare some newer derivatives and study their *in vivo* action on malarial parasites. In order to optimize the antimalarial activity, the synthesized compounds were subjected to QSAR study using linear free energy related regression analysis. The results are reported in this paper.

Since the OH group at position-4 of of quinoline ring was shown to be phenolic in nature, its esterification followed by hydrazinolysis was carried out smoothly to yield the required hydrazides (**2**). Condensation of these hydrazides with suitable aryl isothiocyanates resulted in the formation of 1-(2′-methyl-6′-substituted quinolin-4′-yloxyacetyl)-4-(*p*-substituted phenyl)-3-thiosemicarbazides (**3**; Table 1). These thiosemicarbazides on refluxing with 2*N* NaOH underwent cyclization to afford the corresponding 5-(2′-methyl-6′-substituted quinolin-4′-yloxymethyl)-4-(*p*-substituted phenyl)-4*H*-1,2,4-triazole-3-thiols (**4a-h**) which on condensation with alkyl bromides yielded 3-alkylmercapto-5-(2′-methyl-6′-substituted quinolin-4′-yloxymethyl)-4-(*p*-substituted phenyl)-4*H*-1,2,4-triazoles (**4i-x**; Table 2).

Antimalarial activity

All biological studies were carried out on 5-10 groups of albino mice of either sex weighing 20 ± 2 g; each group contained 8 animals. Each mice received a single inoculum of approximately 10^7 infected red cells.

Four days suppressive test of blood schizonotocidal action against P. yoelli nigeriensis in mice[6]

Oral treatment with the compound in suspension was given two hr after infection. Various doses were

Table 1 – Characterization Data of 1-(2′-Methyl-6′-substituted quinolin-4′-yloxymethyl)-4-(*p*-substituted phenyl)-3-thiosemicarbazides (**3**)

Compd*	R	R_1	m.p. C	Mol. formula	N (%) Found	N (%) Calc
3a	H	H	222	$C_{19}H_{18}N_4O_2S$	15.2	15.3
3b	H	Cl	227	$C_{19}H_{17}ClN_4O_2S$	13.3	14.0
3c	H	Br	165	$C_{19}H_{17}N_4O_2S$	12.4	12.6
3d	H	OCH_3	202	$C_{20}H_{20}N_4O_3S$	14.2	14.1
3e	OCH_3	H	180	$C_{20}H_{20}N_4O_3S$	14.8	14.1
3f	OCH_3	Cl	215	$C_{20}H_{19}ClN_4O_3S$	13.2	13.0
3g	OCH_3	Br	115	$C_{20}H_{19}BrN_4O_3S$	11.7	11.7
3h	OCH_3	OCH_3	218	$C_{20}H_{19}N_4O_4S$	13.6	13.2

*Compounds were obtained in 52-80% yields

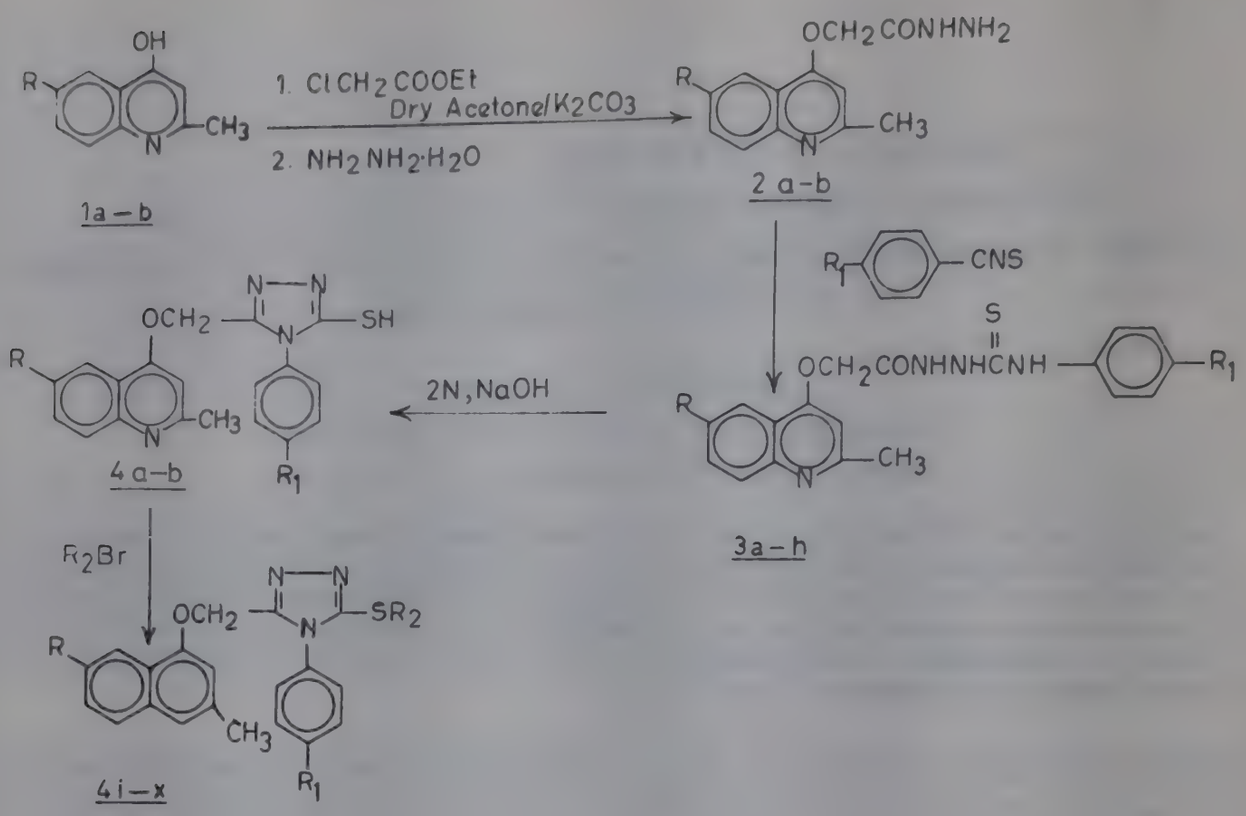

Table 2—Characterization and QSAR Data of 3-Mercapto/Alkylmercapto-5-(2′-methyl-6′-substituted quinolin-4′-yloxymethyl)-4-(*p*-substituted phenyl)-4*H*-1,2,4-triazoles (**4**)

Compd	R	R_1	R_2	m.p. °C	Mol. formula	Antimalarial activity ED_{50} (mg/kg i.v.)	π	MR	−log1/*C*	
									Found	Calc.†
4a	H	H	H	240	$C_{19}H_{16}N_4OS$	45	0	1.03	1.65	1.41
4b	H	Cl	H	280-83	$C_{19}H_{15}ClN_4OS$	110	0.70	6.06	2.04	1.63
4c	H	OCH_3	H	224-28	$C_{20}H_{18}N_4O_2S$	15	−0.02	7.93	1.17	1.40
4d	H	Br	H	270-71	$C_{19}H_{15}BrN_4OS$	32	0.86	8.94	1.50	1.67
4e	OCH_3	H	H	198-99	$C_{20}H_{18}N_4O_2S$	10	−0.02	7.93	1.00	1.40
4f	OCH_3	Cl	H	265-66	$C_{20}H_{17}ClN_4O_2S$	90	0.68	13.93	1.95	1.63
4g	OCH_3	OCH_3	H	256-57	$C_{21}H_{20}N_4O_3S$	20	−0.04	15.77	2.30	1.39
4h	OCH_3	Br	H	290-92	$C_{20}H_{17}BrN_4O_2S$	88	0.84	16.78	2.02	1.68
4i	H	H	C_2H_5	165	$C_{21}H_{20}N_4OS$	35	1.02	10.36	1.54	1.72
4j	H	Cl	C_2H_5	160-62	$C_{21}H_{19}ClN_4OS$	95	2.72	16.06	1.97	1.95
4k	H	OCH_3	C_2H_5	212-14	$C_{22}H_{22}N_4O_2S$	60	0.98	18.20	1.77	1.72
4l	H	Br	C_2H_5	186-88	$C_{21}H_{19}BrN_4OS$	138	1.88	19.21	2.14	2.00
4m	OCH_3	C_2H_5	C_2H_5	214-15	$C_{22}H_{22}N_4O_2S$	85	1.00	18.20	1.93	1.73
4n	OCH_3	Cl	C_2H_5	232	$C_{22}H_{21}ClN_4O_2S$	135	1.70	24.23	2.13	1.95
4o	OCH_3	OCH_3	C_2H_5	204-6	$C_{23}H_{24}N_4O_3S$	80	0.98	26.04	1.30	1.72
4p	OCH_3	Br	C_2H_5	280-81	$C_{22}H_{21}BrN_4O_2S$	70	1.86	27.05	1.94	1.99
4q	H	H	C_4H_9	220-21	$C_{23}H_{24}N_4OS$	120	1.98	19.95	2.08	2.03
4r	H	Cl	C_4H_9	226	$C_{23}H_{23}ClN_4OS$	205	2.68	25.65	2.31	2.25
4s	H	OCH_3	C_4H_9	238-39	$C_{24}H_{26}N_4O_2S$	125	1.96	27.49	2.09	2.03
4t	H	Br	C_4H_9	195-96	$C_{23}H_{23}BrN_4O_2S$	22	2.84	28.50	1.43	2.29
4u	OCH_3	H	C_4H_9	218	$C_{24}H_{26}N_4O_2S$	150	1.96	27.49	2.17	2.03
4v	OCH_3	Cl	C_4H_9	282-83	$C_{24}H_{25}ClN_4O_2S$	210	2.66	33.49	2.32	2.25
4w	OCH_3	OCH_3	C_4H_9	230	$C_{25}H_{28}N_4O_3S$	105	1.94	35.34	1.90	2.02
4x	OCH_3	Br	C_4H_9	292-95	$C_{24}H_{25}BrN_4O_2S$	140	2.84	36.34	2.15	2.29

*Compounds were obtained in 46-67% yield. C, H, and N analyses were within ±0.5% of theoretical values.
†From Eq. (1)

given to different groups of infected mice once daily for four consecutive days. Regular blood microscopical examinations were carried out four days after the infection for ten days post-infection. A range of values of doses were plotted against percentage activity to obtain a dose-activity curve for the calculation of 50% affective dose (ED_{50}). The values thus obtained are given in Table 2.

Quantitative structure activity relationship

There are three major factors[7] involved in drug receptor interaction, hydrophobic, steric and electronic, amongst them only the two physiochemical parameters, hydrophobic ($\log P$ or π) and steric (MR) were considered. The overall liphilicity ($\log P$) is responsible for the transportation of drug to the active site and its hydrophobic association therein. Another parameter, molecular refractivity (MR)[8,9] has been reported to be a measure of steric bulk and polar space at receptor. In the present investigation only the effect of variation of the side chain on the triazole nucleus has been studied. It has often been observed[10–12] that there is a high colinearity of MR and $\log P$. Therefore, it is difficult to distinguish between the nonspecific interaction in polar space or steric interaction (MR) and the hydrophobic space ($\log P$). It can be due to dependency of $\log P$ and MR to a certain extent on molar volume. Moreover, MR and $\log P$ are giving almost the same information with regression equations. Because of more reliability of $\log P$ data as compared to MR, due to experimental verification, equations (1) and (2) were obtained with $\log P$.

The best equation involving different combinations of substituent constant for all the compounds of the series was obtained with quantitative relationship of π with biological activity (Eq. 1) and further the coefficient of π and π^2 and the value of constant term permitted the inclusion of all the compounds of this series in one congeneric series.

$$-\log\frac{1}{C} = 0.314\pi + 1.408 \quad \ldots (1)$$

$(n=24,\ r=0.86,\ s,=0.19)$

$$-\log\frac{1}{C} = 1.85\pi + 0.578\pi^2 + 0.309 \quad \ldots (2)$$

$(n=24,\ r=0.43,\ s=0.76)$

The above equations (1) and (2) describe respectively the linear and parabolic correlations of lipophilicity with antimalarial activity (blood schizontocidal). In the above equations, C represents the concentration of the drug, n is the number of compounds, r is correlation coefficient and s is standard deviation.

The high correlation coefficient ($r=0.86$) and low standard deviation ($s=0.19$) of Eq. (1) point to the linear correlation between lipophilicity and antimalarial activity. There is a good agreement between observed and calculated biological activities using Eq. (1) (Table 2). From the foregoing discussion it can be concluded that lipophilicity plays a major role in eliciting the antimalarial activity as has been observed earlier[13].

Experimental Procedure

All m.ps were recorded in open capillary tubes and are uncorrected. IR spectra were taken in KBr on Perkin-Elmer 137 and 177 spectrophotometers (ν_{max} in cm^{-1}) and PMR spectra on Varian A-60D and Perkin-Elmer R-32 spectrophotometers using TMS as internal standard (chemical shifts in δ, ppm). 2-Methyl-6 substituted-4-hydroxyquinolines (**1a**,**b**) were prepared by the method described in literature[14].

6-Substituted (2-methylquinolin-4-yloxy)acetic acid hydrazides (**2a**,**b**)

4-Hydroxy-2-methylquinoline (**1a**) (15.9 g, 0.1 mol) and anhyd. K_2CO_3 (0.15 mol) were dissolved in an excess of acetone (dry) and the solution was heated for 30 min. Ethyl chloroacetate (10.6 g, 0.1 mol) was then added to the refluxing solution and the mixture heated for 24 hr, excess solvent removed and residue refluxed with ethanol (75 ml) and hydrazine hydrate (0.2 mol) for another 18 hr. The excess of ethanol was distilled off under reduced pressure. The crude product which separated out on cooling in an ice-bath was filtered and crystallized from ethanol to give (2-methylquinolin-4-yloxy)acetic acid hydrazide (**2a**), m.p. 242°, yield 12.5 g (54%); IR (KBr): 1690 (C=O), 3100 (NH), 1620 (CN), 3300 (NH_2); PMR ($CDCl_3$): 4.3-4.4 (*s*, 2H, OCH_2), 6.8-7.7 (*m*, 5H, Ar-*H*), 1.15-1.35 (*s*, 3H, CH_3), 4.24 (*d*, 2H, NH_2), 9.4 (*s*, 1H, CONH).

Following a similar procedure (6-methoxy-2-methylquinolin-4-yloxy)acetic acid hydrazide (**2a**) was prepared form 4-hydroxy-6-methoxy-2-methylquinoline (**2b**) (18.9 g, 0.1 mol) and crystallized from ethanol, m.p. 232°, yield 11.8 g (49%); IR (KBr): 1670 (C=O), 3100 (NH), 1610 (CN), 3310 (NH_2).

(1-2′-Methyl-6′-substituted quinolin-4′-yloxy-acetyl)-4-(p-substituted phenyl)-3-thiosemicarbazides (**3**; *Table* 1).

Equimolar quantities of **2a** (2.3 g, 0.01 mol) and *p*-chlorophenyl isothiocyanate (1.7 g, 0.01 mol) in abs. ethanol (40 ml) were refluxed for 4 hr. The crude product that separated out after removal of solvent by distillation under reduced pressure was filtered, washed several times with cold ethanol and pet. ether to give 1-(2′-methylquinolin-4′-yloxyacetyl)-4-(*p*-chlorophenyl)3-thiosemicarbazide (**3b**), m.p. 222°, yield 2.25 g (56.2%); PMR (DMSO-d_6): 2.2 (*s*, 3H,

CH_3), 3.3(*s*, 2H, OCH_2), 6.9-7.2(*m*, 9H, Ar-*H*), 8.1-8.9 (*m*, 3H, 3NH).

Other members of the series were prepared in a similar manner.

5-(2'-Methyl-6'-substituted-quinolin-4'-yloxy-methyl)-4-(p-substituted phenyl)-4H-1,2,4-triazol-3-thiols (**4a-h**; *Table* 2)

A solution of the thiosemicarbazide **3b** (2.0 g, 0.005 mol) in 2*N* NaOH was refluxed for 3 hr, cooled filtered and filtrate acidified with dil. HCl. The precipitate was filtered, washed with water and crystallized from ethanol to give 5-(2'-methylquinolin-4'-yloxymethyl)-4-phenyl-4*H*-1,2,4-triazol-3-thiol (**4b**), m.p. 240°, yield 1.5 g (75%), PMR ($CDCl_3$): 1.1-1.5(*s*, 3H, CH_3), 3.8-4.1(*s*, 2H, OCH_2), 6.8-7.8(*m*, 9H, Ar-*H*).

Other members of the series were prepared in a similar way.

3-Alkylmercapto-5-(2'-methyl-6'-substituted quinolin-4'-yloxymethyl)-4-(p-substituted phenyl)-4H-1,2,4-triazoles (**4i-x**; *Table* 2)

Equimolar quantities of **4b** (0.8 g, 0.002 mol) and ethyl bromide (0.2 g, 0.002 mol) were refluxed for 6 hr on a sand-bath, poured slowly onto crushed ice-HCl (1:1, 100 ml) and crude product was filtered, washed with cold water, dried in air and crystallized from ethanol to give 3-ethylmercapto-5-(2'-methylquinolin-4'-yloxymethyl)-4-(*p*-chlorophenyl)-4*H*-1,2,4-triazole (**4j**), m.p. 166°, yield 0.6 g (73%); PMR (DMSO-d_6): 1.1-1.4(*m*, 6H, 2 × CH_3), 3.8-4.2(*m*, 4H, 2 × CH_2), 6.8-7.8 (*m*, 9H, Ar-*H*).

Other members were prepared in a similar way.

Determination of partition coefficient

Partition coefficient for **4a** and **4b** were determined experimentally. The compounds were isolated as free bases and purified by column-chromatography over alumina. The compounds (20 mg) were partitioned between 1-octanol (20 ml) and water (100 ml) on a mechanical shaker till the equilibrium was reached (6 hr). The octanol layer was separated and centrifuged at 250 rpm for 30 min and the concentration of the compounds in octanol layer determined before and after partition by measuring absorbance at 250 nm on a Beckmann UV spectrophotometer from the standard curve. The partition coefficient was calculated as $P = (C)$ octanol/(C) water. The log P values for **4a** and **4b** were 3.68 and 4.38 respectively. The π value 0.70 for **4b**, obtained by subtracting log P of **4b** from that of **4a**, was in close agreement with the corresponding calculated value (0.71). The π values for rest of the compounds were calculated using additivity principle according to the literature method[15].

Acknowledgement

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Notes

Claisen Rearrangement of 4,6-Diacetylresorcinol Diallyl Ether: Observation of Loss or (1,5) Sigmatropic Shift of Acetyl Groups

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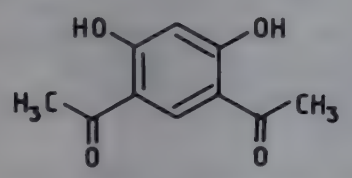
Claisen rearrangement of 4,6-diacetylresorcinol diallyl ether under thermal condition results in a mixture of products, some of which arise by either loss or (1,5) sigmatropic acetyl migration in addition to loss of allyl groups after (3,3) migration. The loss of an acetyl group in this reaction is being reported for the first time.

The *ortho* and *para* Claisen rearrangements of aryl allyl ethers characterised as (3,3) sigmatropic reactions[1], have been extensively studied and reviewed in literature[2]. The rearranged products have been of utmost synthetic value in building up coumaran and chroman systems. Studies involving Claisen rearrangement of aryl allyl ethers, particularly with *ortho* and *para* positions blocked, are still being pursued for understanding the mechanism of the rearrangement and for synthetic value. The Claisen rearrangement of 4,6-diacetylresorcinol diallyl ether (II) forms the subject of this note.

4,6-Diacetylresorcinol (I) prepared in one-pot reaction by the condensation of resorcinol with acetic anhydride in the presence of zinc chloride[3], was allylated with allyl bromide in acetone-potassium carbonate to give II (m.p. 92°) in quantitative yield. The diallyl ether (II) was subjected to thermal Claisen rearrangement by refluxing it in N, N-dimethylaniline for 6 hr. Work-up afforded six compounds, viz. 3, 5-diallyl-2, 4-dihydroxyacetophenone (III, 33%, m.p. 90°, M^+ 232), 5-acetyl-3-allyl-2, 4-dihydroxyacetophenone (IV, 5.9%, m.p. 93-94°, M^+ 234), 5-acetyl-7-allyl-4-hydroxy-2-methyl-(2, 3-dihydro)-benzofuran (V, liquid, 12%, M^+ 232), 4-acetoxy-3, 5-diallyl-2-hydroxyacetophenone (VI, liquid, 6%, M^+ 274), 3, 5-diallyl-2, 6-dihydroxyacetophenone (VII, liquid, 7%, M^+ 232) and 4-acetyl-N, N-dimethylaniline (VIII, 0.13%, m.p. 102°). All these products were fully characterised by their elemental analyses and spectral data (UV, IR, PMR and mass).

The most significant observation is the formation of products arising by the loss of any acetyl or any allyl group. Products (III) and (IV) appeared to have been formed from a common intermediate (A) and III in turn gave V on cyclisation. The products III and V were also obtained in equal quantities when resacetophenone diallyl ether (IX) was subjected to Claisen rearrangement under similar condition. The loss of an acetyl group is being reported for the first



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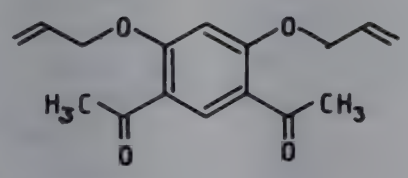

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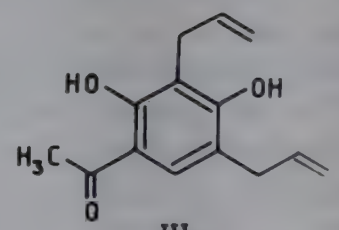

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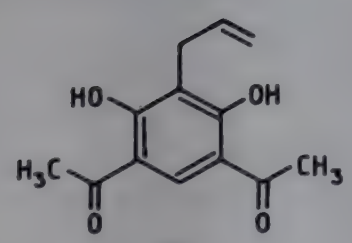

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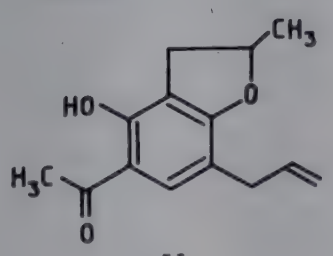

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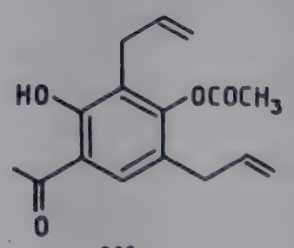

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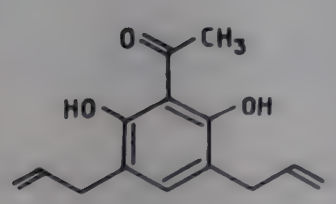

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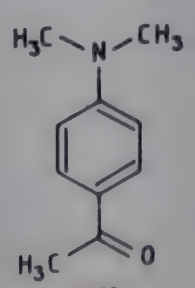

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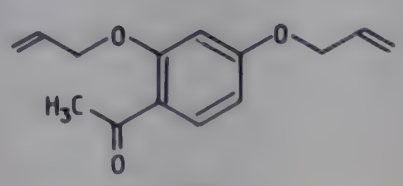

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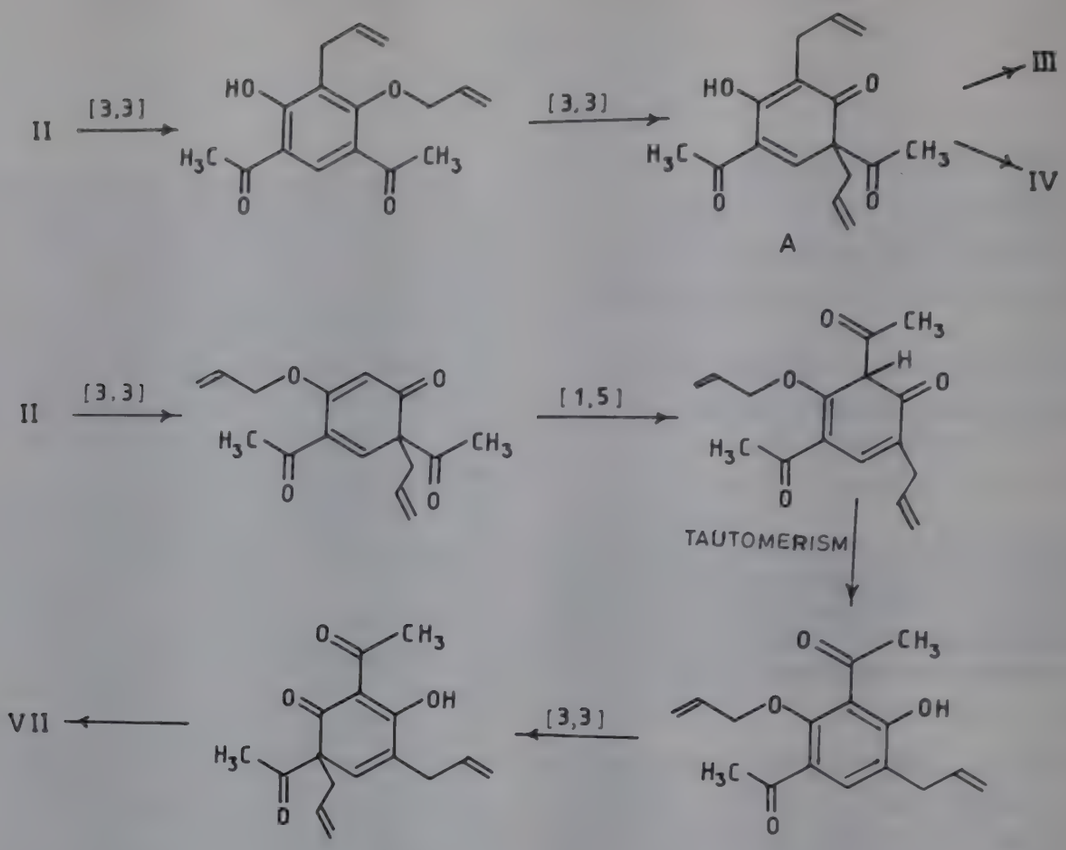

time although the loss of groups such as formyl, carboxy, carbomethoxy and halogen atoms have been noticed earlier. The formation of VI (by mono acetylation of III) and VIII (by acetylation of solvent molecule) provides added proof for the loss of an acetyl group most probably as a cation; its elimination as a radical cannot be totally ruled out. Elimination of allyl groups has also been noticed in a few cases. In these cases the leaving allyl group was shown to participate in further substitution of an existing alkyl or allyl group[4,5]. However, formation of such a derivative was not observed in the present investigation. The formation of VII is more interesting. We believe that it is formed via the thermally allowed (1,5) sigmatropic acetyl migration, as has been observed earlier[6]. Further work is in progress.

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Polonovski Reaction on Laudanosine N-Oxide†

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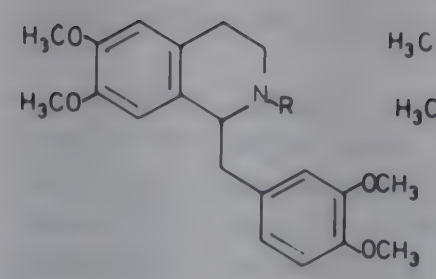
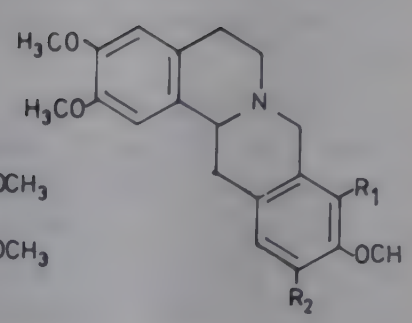
Laudanosine (**1**) when treated with *m*-chloroperbenzoic acid followed by acetic anhydride yields veratryl alcohol (**5**) and the ketoimide (**6**).

Various aspects of Polonovski reaction as well as other reactions, biochemistry and pharmacology of alkaloidal N-oxides have been recently reviewed[1]. In biochemical experiments N-methyltetrahydrobenzylisoquinolines have been converted into tetrahydroprotoberberines[2-5]. One such example is the biotransformation of laudanosine (**1**) into xylopine (**2**), tetrahydropalmatine (**3**) and norlaudanosine (**4**)[3]. In these studies it has also been shown that the N-methyl group of the tetrahydrobenzylisoquinoline ends up as C-8, the 'berberine bridge', in the tetrahydroprotoberberine[4]. These observations led us to undertake the present study involving the use of Polonovski reaction to try to effect the biomimetic cyclization of tetrahydrobenzylisoquinolines to tetrahydroprotoberberines.



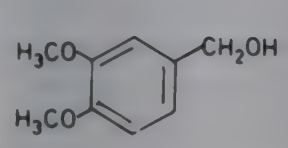
1 R = CH_3

4 R = H



2 R_1 = H, R_2 = OCH_3

3 = R_1 = OCH_3, R_2 = H



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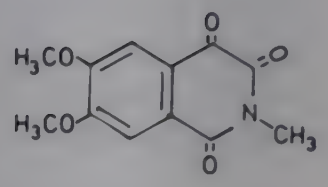

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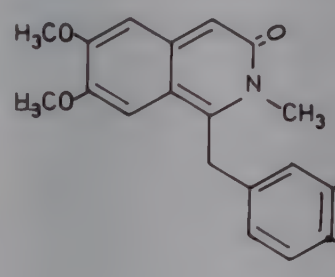

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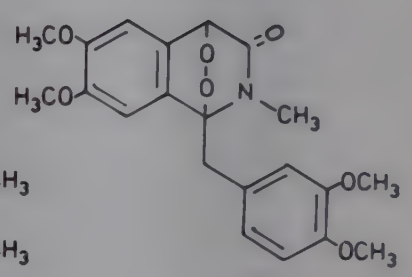

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As a preliminary study, (±)-laudanosine (**1**) was treated with *m*-chloroperbenzoic acid (1.1 equivalent) in dichloromethane at ice temperature for 1 hr. To the same flask excess acetic anhydride was added, the reaction mixture allowed to come to room temperature and stirred for 4 hr at the same temperature. Methanol work-up afforded a residue which yielded a yellow solid, m.p. 257° (from MeOH). The mother liquor was subjected to preparative TLC (SiO_2, 2% MeOH in CH_2Cl_2) to obtain more of the yellow solid (R_f 0.59) (total yield 24%) and veratryl alcohol (**5**) (R_f 0.42; yield 48%). Veratryl alcohol was fully characterized by direct comparison (PMR, IR and co-TLC) with an authentic sample.

The PMR of the yellow solid exhibited one methyl singlet at δ 3.48, two methoxyl singlets at 4.10 and 4.15 and two aromatic singlets of one-proton each at 7.63 and 7.80 (H-5 and H-8). The IR spectrum in KBr displayed bands at 1678, 1700 and 1730 cm^{-1}, indicating the presence of at least three carbonyl functions. The absence of aliphatic protons and the lowfield (δ 3.48) N-methyl signal led to the structure (**6**) (Found: C, 57.1; H, 4.6; N, 5.6. $C_{12}H_{11}NO_5$ requires C, 57.8; H, 4.4; N, 5.6%) for the yellow solid. Additional proof for the structure was provided by its mass spectrum with parent peak at *m/z* 249 (which is also the base peak) and diagnostic peaks at *m/z* 221 $(M-CO)^{\cdot+}$, 206 $(221-CH_3)^{\cdot+}$, 177 $(206-NCH_3)^{+}$, 164 $(M-CONCH_3CO)^{\cdot+}$ and 136 $(164-CO)^{\cdot+}$ and analysis by high resolution mass spectrometry (Calc. for $C_{12}H_{11}NO_5$: 249.06372. Found: 249.06442). Carbon-13 NMR recorded in $CDCl_3$ displayed the following signals: δ 56.11 (NCH_3), 56.73 and 56.83 (2 × OCH_3), 108.52 (C-8), 110.74 (C-5), 123.51 (C-8a), 125.46 (C-4a), 154.16 (C-6), 155.87 (C-7), 157.73 (C-3), 160.56 (C-1) and 170.80 (C-4).

†This paper is dedicated to Prof B R Pai.
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§Present address: c/o Prof W Wiegrebe, Chemie/Pharmazie, Universitat Regensburg, D-8400 Regensburg, West Germany.

Kreighbaum *et al.*[6] had envisaged the formation of **6** by spontaneous oxidation of the free base form of 3(2*H*)-isoquinolone (**7**) via the peroxide (**8**). The isolation of veratryl alcohol (**5**) in the present study indicates that perhaps a similar mechanism operates here also.

Of the three different directions available for Polonovski elimination, only when the N-methyl group loses its proton the cyclization to tetrahydroprotoberberine is possible. However, the isolated products indicate a different direction of elimination and further work is in progress to alter the direction of elimination.

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Synthesis of Purpuritenin-A & 4′-Methylfurano[2″,3″:7,8]flavone†

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2′-Methoxy-4-methylfurano[3″,2″:3′,4′]chalcone (Ia) and 4′-methylfurano[2″,3″:7,8]flavone (III) have been synthesised from the corresponding furano[3′,2′:3,4]acetophenones. Disparity in the observed spectral data for purpuritenin-A and the synthetic product (Ia) suggests revision of the structure for the natural product.

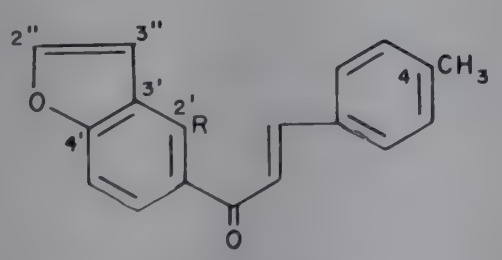
Nanavati and Sinha[1] isolated a furanochalcone from the seeds of *Tephrosia purpurea* (Linn.) Pers and designated it as purpuritenin-A assigning the structure Ia on the basis of its spectral data. Since occurrence of chalcones (flavones) having a methyl substituent in ring-B in the nature is not common[2], we undertook the synthesis of purpuritenin-A to establish its structure unequivocally. The condensation of 2-methoxyfurano[3′,2′:3,4]acetophenone (obtained from 3-allylresacetophenone by ozonolysis, cyclization and methylation[3,4]) with *p*-toluylaldehyde[5] in the presence of alkali yielded purpuritenin-A (Ia), which crystallized from benzene-pet. ether as pale yellow rods, m.p. 132-34°, R_f 0.43 (pet. ether-chloroform; 1:1); UV(CH_3CN): 240, 310 nm; IR(nujol): 1640, 1590, 1360, 1260, 1230, 1180, 1160, 1070, 1050, 985, 820, 750 cm^{-1}; PMR: δ 2.38 (*s*, 3H, CH_3 at C-4), 4.08 (*s*, 3H, OCH_3), 6.98 (*d*, J = 2 Hz, 1H, H-3″), 7.08 (*d*, J = 12 Hz, 2H, H-3 and H-5), 7.55 (*d*, J = 2 Hz, 1H, H-2″), 7.65 (*d*, J = 10.2 Hz, 2H, H-2 and H-6), 7.74 (*d*, J = 9 Hz, 1H, H-6′), 7.1-7.67 (*m*, 3H, H-5′, α-H and β-H); MS: *m/z* 292 (100%), 277 (55), 261 (32), 176 (53), 146 (39), 116 (48), 105 (44), 91 (46), 77 (29).

It is interesting to note that IR and PMR spectral data of the authentic chalcone described here do not concur with those reported earlier[1], suggesting a need for revising the structure for purpuritenin-A. However due to nonavailability of the natural sample a direct comparison (m.m.p. and co-TLC) could not be done.

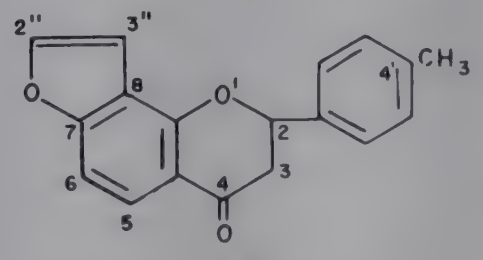
Compound III which crystallized from chloroform-methanol in colourless needles, m.p. 218-20°, R_f 0.47 (benzene-acetone; 4:1) was synthesised from 2-hydroxyfurano[3′,2′:3,4]acetophenone through the corresponding chalcone (Ib) (orange yellow prisms from benzene-methanol, m.p. 150-52°) and flavanone (II) (pale yellow rods from mehthanol-water, m.p. 92-93°). The spectral data of these compounds are as follows:

Chalcone Ib: UV(CH_3CN): 242, 330 nm; IR (nujol): 1635, 1600, 1570, 1470, 1390, 1350, 1285, 1160, 1050, 980, 855, 755 cm^{-1}; PMR: δ 2.36 (*s*, 3H, CH_3), 6.95 (*d*, J = 11.4 Hz, 2H, H-3 and H-5), 6.89 (*d*, J = 3 Hz, 1H, H-3″), 7.5 (*d*, J = 3 Hz, 1H, H-2″), 7.60 (*d*, J = 13.4 Hz, 2H, H-2 and H-6), 7.80 (*d*, J = 12.4 Hz, 1H, H-6′), 7.1-7.6 (*m*, 3H, H-5′, α-H and β-H), 13.78 (*s*, 1H, OH); MS: *m/z* 278 (66%), 263 (25), 260 (16), 188 (51), 187 (18), 162 (28), 161 (100), 133 (34), 117 (37), 105 (30), 91 (26), 77 (21).

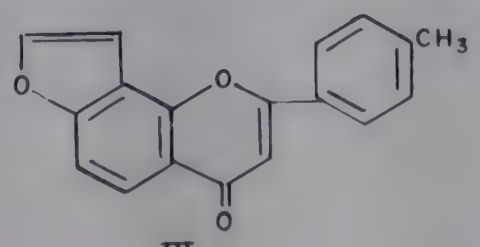
4′-Methylfurano[2″,3″:7,8]flavanone (II): UV(CH_3CN): 212, 238, 325 nm; IR (nujol): 1670, 1610, 1595, 1460, 1380, 1330, 1290, 1250, 1215, 1115, 1100, 1050, 1020, 815, 785, 750 cm^{-1}; PMR: δ 2.37 (*s*, 3H, $-CH_3$), 2.98-3.2 (*m*, 2H, 3-CH_2), 5.4-5.62 (*m*, 1H, H-2), 6.85 (*d*, J = 2 Hz, 1H, H-3′), 6.99 (*d*, J = 9 Hz, 2H, H-3′ and H-5′), 7.19 (*d*, J = 9 Hz, 1H, H-6), 7.34 (*d*, J = 9



Ia R = OCH_3
Ib R = OH



II



III

†NCL Communication No. 3813

Hz, 2H, H-2′ and H-6′), 7.53 (*d*, $J=2$ Hz, 1H, H-2″), 7.84 (*d*, $J=9$ Hz, 1H, H-5); MS: *m/z* 278 (100%), 263 (6), 149 (20), 105 (28), 91 (32), 77 (30).

4′-Methylfurano[2″,3″:7,8]flavone (III): UV(CH_3CN): 220, 265, 302 nm; IR (nujol): 1645, 1595, 1450, 1410, 1400, 1355, 1250, 1210, 1120, 1065, 900, 830, 810, 750, 700 cm^{-1}; PMR: δ 2.45 (*s*, 3H, CH_3), 6.78 (*s*, 1H, H-3), 7.14 (*d*, $J=3$ Hz, 1H, H-3″), 7.24 (*d*, $J=9$ Hz, 2H, H-3′ and H-5′) 7.48 (*d*, $J=9.7$ Hz, 1H, H-6), 7.73 (*d*, $J=3$ Hz, 1H, H-2″), 7.77 (*d*, $J=10$ Hz, 2H, H-2′ and H-6′), 8.1 (*d*, $J=9$ Hz, 1H, H-5); MS: *m/z* 276 (54%), 261 (3), 247 (7), 160 (100), 161 (12), 132 (6), 116 (7), 104 (5), 77 (6).

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Aliphatic Nitro Compounds : Part I—Synthesis of 2,6,10,14-Tetramethylpentadec-2-en-7-one†

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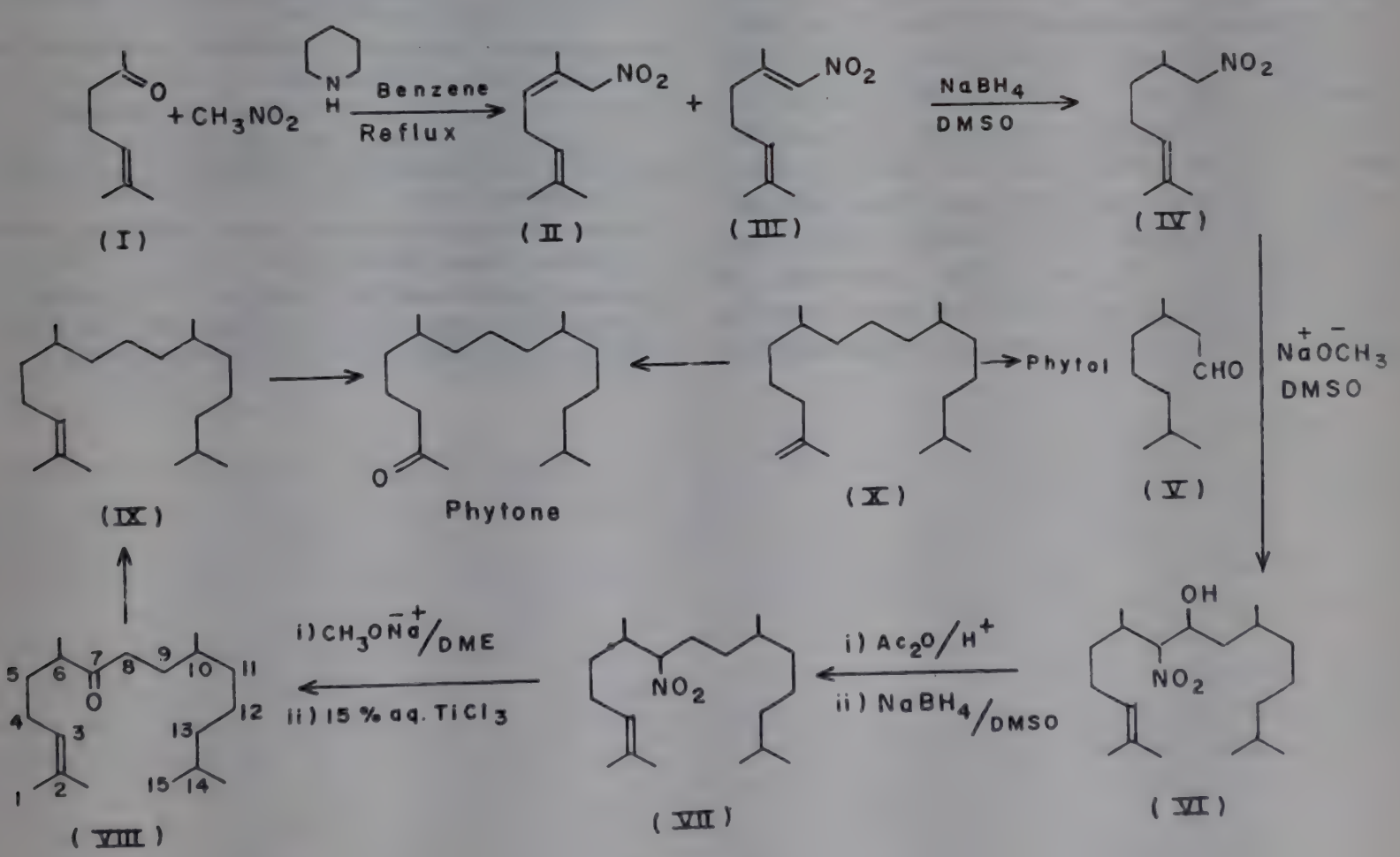
A new ($C_{10}+C_1+C_8$) approach for the synthesis of naturally occurring title compound (C_{19}-hydrocarbon) is described. In the new approach, utilising, methylheptenone (I), nitromethane and dihydrocitronellal (V), the aliphatic nitro group is treated as a carbonyl equivalent.

In recent publications[1-4] we reported new methodologies for the synthesis of naturally occurring C_{19}-hydrocarbon, 2,6,10,14-tetramethylpentadec-2-ene (IX) and norphytene (X), involving (i) the enamine route ($C_{10}+C_{10}-C_1$)[1,4] (ii) Meldrum's acid ($C_{10}+C_1+C_8$)[2]; and (iii) TosMIC route ($C_{10}+C_1+C_8$)[3,4]. Subsequently we reported[5] the conversion of IX into phytone and of X into phytone and phytol.

In the present note we describe a new method, where the aliphatic nitro group is treated as a carbonyl equivalent in the preparation of IX, i.e. in the ($C_8+C_1+C_{10}$) approach. The ketone function is built-up at C-7 from the corresponding nitro compound. The reaction sequence is outlined in Scheme 1.

Methylheptenone (I) and nitromethane in benzene were refluxed for 8 hr under Dean and Stark water separator using piperidene as catalyst to give a product along with some starting I as judged by TLC (solvent:benzene). Compound (I) was removed by distillation under reduced pressure and the residue was chromatographed on silica followed by distillation. This was found to be a mixture of 2,6-dimethoxy-1-nitrohepta-2,5-diene (II, b.p. 108°/10 mm, M^+ 169) as the major product (55%) (kinetic control) and 2,6-dimethyl-1-nitrohepta-1,5-diene (III) as the minor product (8%) (thermodynamic control). The GLC analysis (OV 101, temp. 150°) of II showed two major peaks in the ratio of 25:65 due to *E*− and *Z*− isomers of II; PMR (CCl_4): δ 1.6, 1.7, 1.76 (3*s*, 9H, for methyls on double bonds), 2.73 (*bt*, 2H, J = 6 Hz due to allylic



Scheme 1

†NCL Communication No. 3895

methylene i.e. C-4). The two singlets of δ 4.66 and 4.83 for the protons at C-1 of II are due to the presence of *E*- and Z-isomers (3:7), and broad triplets at δ 5.0 and 5.5 were assigned to olefinic protons at C-5 and C-3, respectively. The above data confirm structure (II). However a small percentage (8%) of III was noted by signals at δ 2.2 (*m*) and 6.8 (*bs*). In order to confirm some of the signals assigned to II and III, nitromethane was condensed, under identical condition, with methylheptanone (hydrogenated I). The compound obtained was characterised (PMR) as 2,6-dimethyl-1-nitro-2-hept-2-ene; PMR (CCl_4): δ 0.98 (*d*, 3H, J = 7 Hz *gem*- dimethyls); 1.82, 1.73 (2*s*, for methyl on double bond, E- and Z-isomers, ratio 3:7), 4.66, 4.83 (2*s*, 2H, protons at C-1, E- and Z-isomers, ratio, 3:7), and 5.5 (*bt* for olefinic protons at C-3), thus confirming the signals assigned for II. Again signals at δ 6.8 and 2.2 indicated the presence of 2,6-dimethyl-1-nitro-hept-1-ene to the extent of about 8% (thermodynamic control).

As it is known that an equilibrium is set between α, β and β, γ-unsaturated nitro compounds in the presence of a base, we thought $NaBH_4$ would act as a base as well as a hydrogenating agent. This was found to be the case. Treatment of a mixture of II and III with $NaBH_4$ in DMSO, according to literature procedure[6] for hydrogenating unsaturated nitro compounds, resulted in the saturated compound 2,6-dimethyl-1-nitro-hept-5-ene (IV) in 85% yield, b.p. 82°/5 mm; M^+ 171; IR (liquid film): 1560 cm^{-1} ($-NO_2$); PMR (CCl_4): δ 0.98 (*d*, 6H, J = 7 Hz, CH_3-CH), 1.56, 1.63 (2*s*, 6H, methyls on double bond), 4.09, 4.22 (2H at C-1, 2*q*, J = 7 Hz), 5.00 (1H, *bt*, olefinic proton). The sodium salt of IV was treated with bisulphite adduct of dihydrocitronellal (V) in DMSO according to literature procedure[7] and the alcohol was obtained in pure form in 36% yield by column chromatography on silica; IR (liquid film): 3450 ($-OH$), 1550 cm^{-1} (NO_2); PMR (CCl_4): δ 0.87 (*d*, 12H, $CH-CH-$, J = 7 Hz), 1.6, 1.67 (2*s*, 6H, methyls on double bond), 4.13 (2H, *m*, $-CHNO_2$, $-CHOH$) and 5.06 (*bt*, olefinic proton). The nitroalcohol was acetylated (Ac_2O/conc. H_2SO_4 one drop) quantitatively and the acetylated product reduced by $NaBH_4$ in DMSO to afford a compound characterised (IR, MS and PMR) as 2,6,10,14-tetramethyl-7-nitro-pentadec-2-ene (VII); MS: *m/z* 311 (M^+); IR (liquid film): 1556 cm^{-1} ($-NO_2$); PMR (CCl_4): δ 0.80 (*d*, 12H, CH_3-CH-, J = 7 Hz), 1.52, 1.58 (2*s*, 6H methyls on double bond), 4.18 (*m*, 1H, $-CHNO_2$), 5.00 (*bt*, 1H, olefinic proton). VII was treated with NaOMe/DME first and to this 15% aq. $TiCl_3^8$ (4 eq) was added and stirred for 15 hr to give the 2,6,10,14-tetramethylpentadec-2-ene-7-one (VIII) in 80% yield, b.p. 155°/1 mm; MS: *m/z* 280, 198, 169, 126, IR (liquid film): 1720 cm^{-1} ($>C=O$); PMR (CCl_4): δ 0.89 (*d*, 9H, CH_3-CH-, J = 7 Hz), 1.05 (*d*, 3H, J = 7 Hz, CH_3 to $>C=O$), 1.56, 1.65 (2*s*, 6H, methyls on double bond), 5.00 (*bt*, 1H, olefinic). Huang-Minlon reduction of VIII to IX is reported[4] earlier.

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Reactions of Aromatic Diazonium Salts with Diethyl Sodiomalonate

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Benzenediazonium chloride and *m*-toluenediazonium chloride react with sodium salt of diethyl malonate in aqueous ethanol to give the coupling products (I and V) as the major products, along with other products (II, III, IV and VI) apparently derived from the coupling products. All the products obtained have been fully characterised by IR and PMR data.

Decomposition of substittuted benzenediazonium chlorides in water is known to be first order and involves the formation of aryl carbonium ion in the rate-determining step. The aryl carbonium ion rapidly combines with nucleophiles present in the medium to give the substitution products[1]. Substitution products like $PhCH_2COOH$ (ref. 2), $PhCH_2NO_2$ (ref. 3) and *p*-$O_2N-C_6H_4C\equiv CH$ (ref. 4) from similar reactions are also reported. However, coupling reactions of diazonium salts to give azo compounds appear to be more common and in the above reactions also azo compounds come out as the major reaction products. In order to make the substitution reaction as the major pathway, treatment of diazonium salts with strong nucleophiles in polar medium is expected to be more appropriate. We report herein our results on the reactions of benzenediazonium chloride and *m*-toluenediazonium chloride with diethyl sodiomalonate in aqueous ethanol.

Diethyl sodiomalonate (1 mol) in ethanol was treated with an aqueous solution of aromatic diazonium salt (3 mol) ($PhN_2^+Cl^-$, *m*-$CH_3C_6H_4N_2^+Cl^-$) at 0-5°C to give a deep red solution which on usual work-up (washing with 5% aq. $NaHCO_3$, H_2O and extraction with ether) gave a dark red semisolid mass. Chromatography of the crude product over silica gel followed by preparative TLC gave compounds (I) (m.p. 76-77°), (III) (m.p. 130-31°) and (IV) (m.p. 82-83°) from the reaction with benzenediazonium chloride in 40%, 13% and 15% yields respectively. Compound (II) (m.p. 114-15°) was isolated from the alkaline washings in 12% yield. Similarly from *m*-toluenediazonium chloride were obtained compounds (V) and (VI) in 19% and 18% yields, respectively.

$R-NH-N=C(COOEt)_2$

$R-NH-N=C(R')COOEt$

I, $R=C_6H_5$
V, $R=m$-$CH_3-C_6H_4$

II, $R=C_6H_5$; $R'=H$
III, $R=C_6H_5$; $R'=H$
IV, $R=R'=Ph$
VI, $R=R'=m$-$CH_3C_6H_4$

In both the reactions the coupling products (I) and (V) were the major products. Compound (II) was obviously produced by hydrolysis of one of the ester functions of I and III followed by decarboxylation. Compound (IV) was probably formed by the attack of the nucleophile of the partially hydrolysed coupling product on a second diazonium chloride molecule causing a substitution on benzenediazonium chloride. Compound (VI) was similarly formed from the second reaction. All the products (I-VI) were fully characterized by IR, PMR and mass spectral data. Compound (I) was obtained as a pink red crystalline solid; IR: 3270 (N−H), 1705 (conjugated ester) cm^{-1}, PMR: δ 7.2-6.9 (*m*, 6H; 5H aromatic and 1 NH), 4.40 (*q*, 4H, $2\times OCH_2-$), 1.4 (*t*, 6H, $2\times CH_3$); M^+ 264 ($C_{13}H_{16}N_2O_4$). Meyer[5] isolated I as an oily substance and failed to crystallise the compound. Hantzsch[6] reported the preparation of I by reacting diethyl mesoxalate with phenyl hydrazine but did not report its melting point.

Compound (II) was obtained as needle shaped crystalline solid; IR: 3200 (br, O−H) 3135 (N−H), 1700 (C=O of COOH), 1705 (C=O of conjugated ester) cm^{-1}; PMR: δ 7.5-7.2 (*m*, 5H, aromatic), 5.53 (*s*, 1H, CH of tautomer), 4.45 (*q*, 2H), 1.44 (*t*, 3H); M^+ 236 ($C_{11}H_{12}N_2O_4$). Its melting point coincides with the m.p. reported for partial hydrolysis product of phenylhydrazone of diethyl mesoxalate which has the same structure as II. Compound (III), was obtained as pale yellow crystals; IR: 3260 (N−H), 1702 (conjugated ester) cm^{-1}; PMR: δ 7.4-7.1 (*m*, 6H; 5H aromatic and 1 NH), 5.3 (*s*, 1H), 4.45 (*q*, 2H), 1.3 (*t*, 3H); M^+ 192 ($C_{10}H_{12}N_2O_2$).

Compound (IV) was obtained as yellowish red crystals; IR: 3280 (N−H), 1695 (conjugated ester) cm^{-1}; PMR: δ 7.7-7.2 (*m*, 11H; 10H aromatic and 1NH), 4.35 (*q*, 2H), 1.4 (*t*, 3H); M^+ 268 ($C_{16}H_{16}N_2O_2$) (Found: C, 71.4; H, 6.1; N, 10.0. $C_{16}H_{16}N_2O_2$ requires C, 71.6; H, 6.0; N, 10.4%). Compound (V) was obtained as a deep red low melting solid; IR: 3230 (N−H), 1715 (conjugated ester) cm^{-1}; PMR: δ 7.7-6.85 (*m*, 5H; 4H aromatic and 1NH), 4.18 (*q*, 4H), 2.35 (*s*, 3H), 1.35 (*t*, 6H); M^+ 278 ($C_{14}H_{18}N_2O_4$). Compound (VI) was also

obtained as deep red low melting solid; IR: 3215 (N −H), 1705 (conjugated ester) cm^{-1}; PMR: δ 7.7-6.9 (*m*, 9H; 8H aromatic and 1 NH), 4.35 (*q*, 2H), 2.4 (*s*, 3H), 2.35 (*s*, 3H), 1.3 (*t*, 3H); M^+ 296 ($C_{18}H_{20}N_2O_2$).

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Reaction of Acetone with 2-Ketotetrahydroquinoxaline under Free Radical Conditions: An Easy Synthesis of 3-(2-Oxopropyl)-2(1*H*)-quinoxalinone

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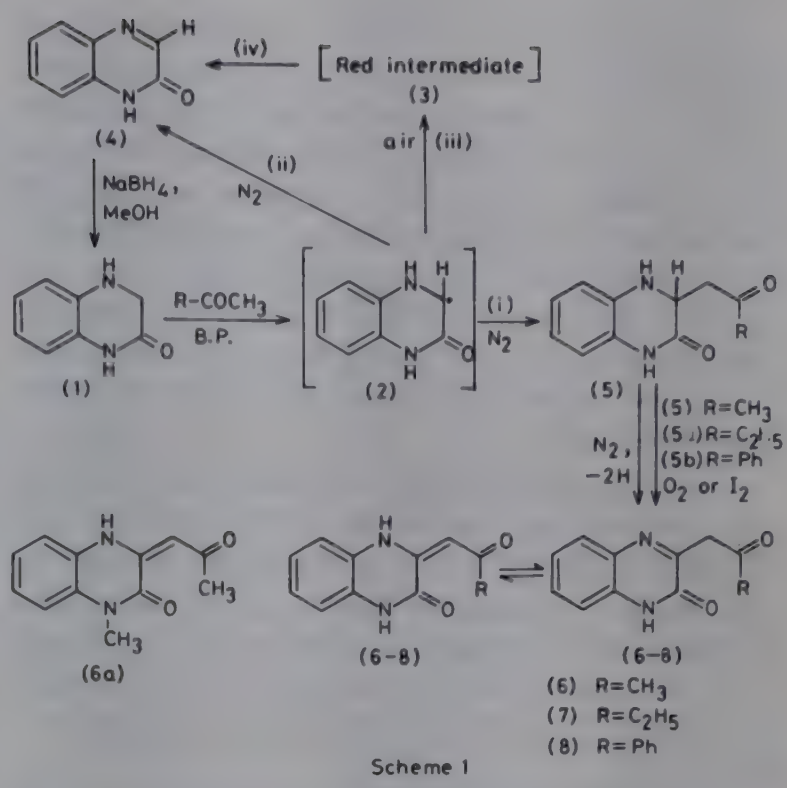
Acetone under free radical conditions reacts with 2-ketotetrahydroquinoxaline (**1**) to produce 3-(2-oxopropyl)-2(1*H*)-quinoxalinone (**6**) and 2-hydroxyquinoxaline (**4**), probably through a common intermediate **2** in nitrogen atmosphere. However in the presence of air **2** is converted into another red coloured intermediate (**3**) which in turn changes to **4**. Reaction of **1** with ethyl methyl ketone and acetophenone produces 3-(2-oxobutyl)-2(1*H*)-quinoxalinone (**7**) and 3-(2-oxo-2-phenylethyl)-2(1*H*)-quinoxalinone (**8**) respectively.

2-Oxo-1,2-dihydro-3-quinoxalinyl ketones have been prepared earlier by different routes[1-4]. However, no attempt has so far been made to prepare such compounds by direct condensation of ketones with the easily prepared 2-keto-1,2,3,4-tetrahydroquinoxaline (**1**).

It is known that the substitution of quinoxaline takes place at C-3 when it is irradiated in ether, methanol or ethanol through a quinoxaline radical intermediate. Recently Nishio and Omote[5] postulated that the formation of reductive dimers of 2-hydroxyquinoxaline (**4**) involves an intermediate anion radical. Therefore, we became interested in the utilization of this approach to prepare 2-oxo-1,2-dihydro-3-quinoxalinyl ketones. For this purpose we selected as probe the reaction between acetone and **1** in the presence of benzoyl peroxide to give 3-(2-oxopropyl)-2(1*H*)-quinoxalinone (**6**) in 40-45% yield. The other two ketones tried were ethyl methyl ketone and acetophenone to prepare **7** and **8** in about 40-45% yield. 2-Hydroxyquinoxaline (**4**) was found to be the other product in each case.

To understand the reaction mechanism we studied the reaction between acetone and **1** under different conditions (Table 1) and found that **4** and **6** were formed form the same intermediate, probably 2-ketotetrahydroquinoxaline radical **2**; (Scheme 1) under nitrogen atmosphere. It is clear from our observation that when **1** and benzoyl peroxide were taken in acetone in 1 : 1 molar ratio and refluxed for 1 hr under nitrogen atmosphere 40-45% of **6** was formed along with about 30% of **4**. However, when the ratio was changed to 1 : 2 under identical reaction conditions, **4** was formed in



Scheme 1

Table 1—Reaction Conditions for the Formation of **6** and **4** and Their Yields

Expt No.	Molar ratio between 1 and BP*	Reaction conditions†	Yield‡ (%) 6	Yield‡ (%) mixture 4	Colour of reaction
		Ketone used, Acetone			
1	1:3	Air, r.t., 24 hr	5	35	Reddish yellow
2	1:3	N_2, r.t., 24 hr	20	22	yellow
3	2:1	Air, r.t., 24 hr	8	40	Reddish yellow
4	1:1	Air, r.t., 24 hr	25	15	Reddish yellow
5	1:1	N_2, r.t., 24 hr,	35-40	40	Yellow
6	1:1	N_2, , 1 hr	40-45	30	Yellow
7	1:2	N_2, 1 hr	5	70	Yellow
8	1:1	N_2, , I_2 (Cat.)	25	40	Reddish yellow
9	1:1	Air, HCl, MeOH	33	40	Reddish yellow

*BP = Benzoyl peroxide.
†r.t. = Room temperature; Cat. = catalyst.
‡ = Isolated yield.

almost 90% yield. The oxidation of **1** by metal ion in the absence of oxygen was observed earlier by us[6]. When the reaction was carried out in the presence of air, the yield of **6** was reduced to 25% with the formation of some acetone insoluble red compounds that gradually converted into **4** in the presence of air. Although no such red compound was formed under nitrogen atmosphere, during work-up the crude reaction mixture slowly turned red.

Therefore, we would like to propose that while under nitrogen atmosphere the reaction paths (i) and (ii) are operative only, in the presence of air path (iii) is

also in operation to form the red intermediate **3** (Scheme 1) which is oxidised by air to **4** by path (iv). It explains the lower yield of **6** when the reaction is carried out in the presence of air.

Iodine is known to oxidise **1** to **4**. When catalytic amount of iodine was added (3% w/w) to an equimolar mixture of **1** and benzoyl peroxide and refluxed under nitrogen atmosphere for 1 hr, 60% of **4** and 25% of **6** were formed without the formation of the red intermediate **3**. This clearly demonstrates that **6** and **4** are formed from the same intermediate **2**.

In fact we observed a spot on TLC very close to **1** which could be due to **2** but as it was very close to both **1** and **4** we could not isolate it in pure form and study its constitution.

2-Hydroxyquinoxaline **4** was identified by m.m.p. determination and comparison of IR, PMR, UV and MS data with those of an authentic sample. 3-Substituted quinoxalines **6**, **7** and **8** were also characterized by comparisons of m.ps and IR, UV and PMR data with those given in literature[1,4]. The mass spectra of **6**, **7** and **8** have prominent molecular ion peaks.

Compound **6** was methylated by the known method[3] to give 1-methyl-3-(2-oxopropyl)-2(1*H*)-quinoxalinone (**6a**), the m.p.[1] and UV[8] spectrum of which agreed well with those given in literature. Reduction of **6** with Zn/HCl gave 3-(2-oxopropyl) 1,2,3,4-tetrahydro-2-quinoxalinone (**5**). Although **5** had a tendency to undergo aerial oxidation to **6** it was possible to isolate it in almost pure state by preparative TLC and record its UV spectra. The λ_{max} at 303 nm confirmed that it had a 2-keto-1,2,3,4-tetrahydro-quinoxaline (**1**) moiety. This compound underwent oxidation slowly to **6** in the presence of air (24 hr) (TLC) and fast in the presence of I_2 (few minutes).

3-*Substituted* 2(1*H*)-*quinoxalinones* **6**, **7** *and* **8**: *General procedure*

A mixture of 2-oxo-tetrahydroquinoxaline **1** (0.02 mol), benzoyl peroxide (0.02 mol) and the appropriate ketone (~35 ml) was left overnight under nitrogen atmosphere/air, the solvent removed under reduced pressure, the crude product passed through a silica gel coloumn and eluted with different mixtures of EtOAc and benzene. Elution with EtOAc-benzene (1 : 4) gave **6**, **7** or **8**. Elution with EtOAc-benzene (3 : 7) furnished **1**, **4** and the unidentified product **2**. Elution with 1 : 1 mixture of EtOAc-benzene gave **3** and **4**. The characterization data of **6-8** are given below.

3-(2-*Oxopropyl*)-(1*H*)-*quinoxalinone* (**6**)

Yellow solid, m.p. 255-56° (lit.[1,4], m.p. 257°), UV (MeOH)[8]: 374 (ε 15000), 395 (ε 20308) and 417 nm (ε 13750); IR (KBr): 1700, 1627 and 1590 cm^{-1}; PMR[8] ($CDCl_3$/DMSO-d_6): δ 12.5 (brs, 1H, NH), 7.17-7.0 (*m*, 4H, Ar-*H*), 6.0 (*s*, 1H, olefinic H), 4.2 (*s*, 1H, tautomeric H) and 2.06 (*s*, 3H, $COCH_3$); MS: (*m/z* 202 (M^+; 36.7%), 187 ($M-CH_3$, 28.8%), 160 ($M-COCH_2$; 15.2%), 159 ($M-COCH_3$, 10.6%).

1-*Methyl*-3-(2-*oxopropyl*)-2(1*H*)-*quinoxalinone* (**6a**)

Yellow solid, m.p. 186° (lit.[1], m.p. 187°); UV (MeOH)[7]: 372 (ε 21166), 394 (ε 23760), 416 nm (ε 16200); IR (KBr) 1663, 1610, 1590 cm^{-1}; PMR ($CDCl_3$): δ 7.3-7.4 (*m*, 4H, Ar-*H*), 6.2 (*s*, 1H, olefinic H), 3.5 (*s*, 3H, $N-CH_3$) and 2.06 (*s*, 3H, $-COCH_3$); MS: *m/z* 216 (M^+; 33.2%), 201 ($M-CH_3$; 30.3%), 174 ($M-COCH_2$; 20.5%), 173 ($M-COCH_3$; 10.7%).

3-(2-*Oxobutyl*)-2(1*H*)-*quinoxalinone* (**7**)

Yellow solid, m.p. 227° (lit.[4], m.p. 203-5°), UV (MeOH): 372 (ε 16232), 392 (ε 21840) and 414 nm (ε 15652). IR (KBr): 1680, 1615 and 1580 cm^{-1}; PMR ($CDCl_3$/DMSO-d_6): δ 13.0 (br *s*, 1H, NH), 11.76 (br *s*, 1H, Ph-OH), 7.4-6.8 (*m*, 4H, Ar-*H*), 6.0 (*s*, 1H, $-HC-C=O$), 4.4 (*s*, 1H, tautomeric-H) and 1.05 (*t*, 3H, $-CH_3$); MS: *m/z* 216 (M^+; 21.4%), 187 ($M-C_2H_5$; 30.7%), 160 ($M-C_2H_4CO$; 16.8%).

3-*Phenyl* 2-(1*H*)-*quinoxalinone* (**8**)

Yellow solid, m.p. 268° (lit., m.p. 267°), UV (MeOH): 392 (ε 15492), 414 (ε 21830) and 438 nm (ε 19044); IR (KBr): 1680, 1615 and 1587 cm^{-1}; PMR (DMSO-d_6): δ 8.7.0 (*m*, 9H, Ar-*H*), 7.82 (*s*, 1H, olefinic H); MS: *m/z* 264 (M^+ 44.4%), 235 ($M-CHO$; 15.5%), 187 ($M-C_6H_5$; 13%), 159 ($M-C_6H_5CO$; 9.5%).

3-(2-*Oxopropyl*)-1,2,3,4-*tetrahydro*-2-*quinoxalinone* (**5**)

3-(2-Oxopropyl)-2(1*H*)-quinoxalinone (**6**) (25 mg) was reduced with Zn/dil.HCl and the reaction mixture extracted with benzene. It was concentrated under reduced pressure and subjected to preparative TLC on silica gel using acetone-benzene (1 : 4) as irrigant. The product (**5**) appeared just below the yellow spot of **6**; UV (MeOH): 303 nm.

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7 Compound **3** was found little contaminated with **4**; UV (MeOH), PMR (DMSO-d_6) and IR (KBr) were found identical with those of **4**.

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Condensation of Quinoline-5,6-diamine with Ketones

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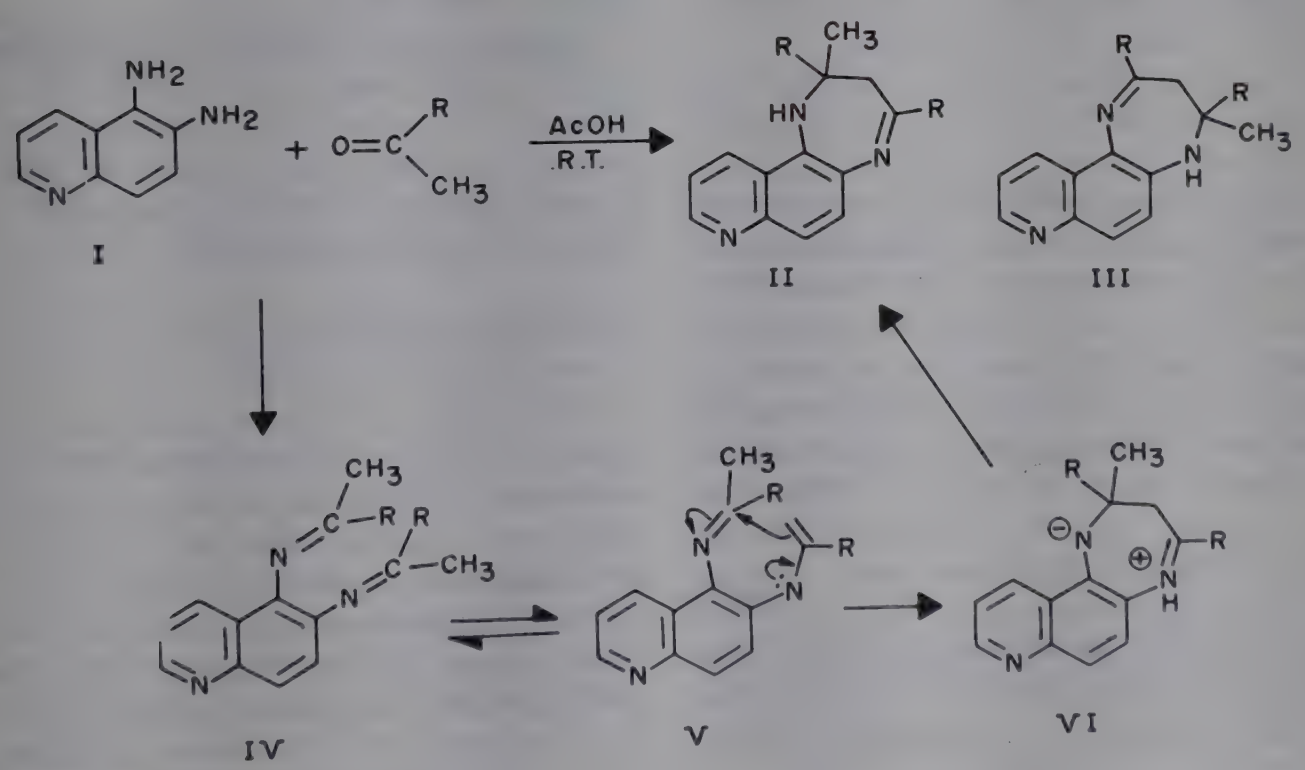
Condensation of quinoline-5,6-diamine (I) with ketones in acetic acid results in the formation of 2,2,4-trialkyl/aryl-2,3-dihydro-1*H*-[1,4]diazepino[2,3-*f*]quinolines(II) and 2-substituted imidazo[4,5-*f*]quinoline derivatives (VI-VIII). The nature of the product obtained varies with the nature of ketone. The formation of the products in these reactions has been rationalised.

The formation of imidazo[4,5-*f*]quinolines in the reaction of quinoline-5,6-diamine(I) with aldehydes[1,2] and acids[3] was reported by us earlier. With diketones, I has been shown to afford pyridoquinoxaline[4,5]. We report here the results obtained in the reaction of I with different mono ketones.

I on reaction with ethyl methyl, *n*-propyl methyl, isopropyl methyl, *t*-butyl methyl and phenyl methyl ketones in 1:2 molar proportion yielded the corresponding 2,2,4-trialkyl/aryl-2,3-dihydro-1*H*--[1,4]diazepino[2,3-*f*]quinolines (IIa-e). Cycloheptanone on reaction with I gave 8,9,10,11,12,12a-hexahydrospiro[cyclo-hepta-1′,2′:5,6][1,4]diazepino-[2,3-*f*]quinoline-13(12*H*), 1′-cycloheptane] (IIf) which may also be named as 3′,4′-cycloheptanospiro[cycloheptane-1,2′-[1*H*]-[1,4]diazepino[2,3-*f*]quinoline]. The formation of II, instead of isomeric 2,4,4-trisubstituted-5*H*-[1,4]diazepino[2,3-*f*]quinolines (III) finds support from the work of Ratnam *et al.*[6] who obtained 1,5-benzodiazepine derivatives in the reaction of benzene-1,2-diamine with cyclopentanone. Further, of the two tautomeric forms (IV and V) possible for dianil, V may preferentially be formed to give II on cyclisation via the transition state which is energetically more feasible due to maximum dispersal of negative charge on the N-5 of quinoline (Chart 1).

However, the reaction of I with dibenzoylmethane in equimolar proportions gave 2,4-diphenyl-[1,4]dizepino[2,3-*f*]quinoline.

Dibenzyl ketone on reaction with I either in gl. acetic acid or in the absence of any solvent at 200°C for 3 hr yielded 2-benzyl-3*H*-imidazo[4,5-*f*]quinoline (VI), identical with an authentic sample (m.p., m.m.p., co-IR) synthesised by the condensation of I with phenylacetic acid in 4*N* HCl[3]. The formation of VI is explained in Chart 2. This finds support from Elderfield's[7] report on the reaction of benzene-1,2-diamine with dibenzyl



R=-C_2H_5, n-C_3H_7, i-C_3H_7, t-C_4H_9, -C_6H_5

CHART 1

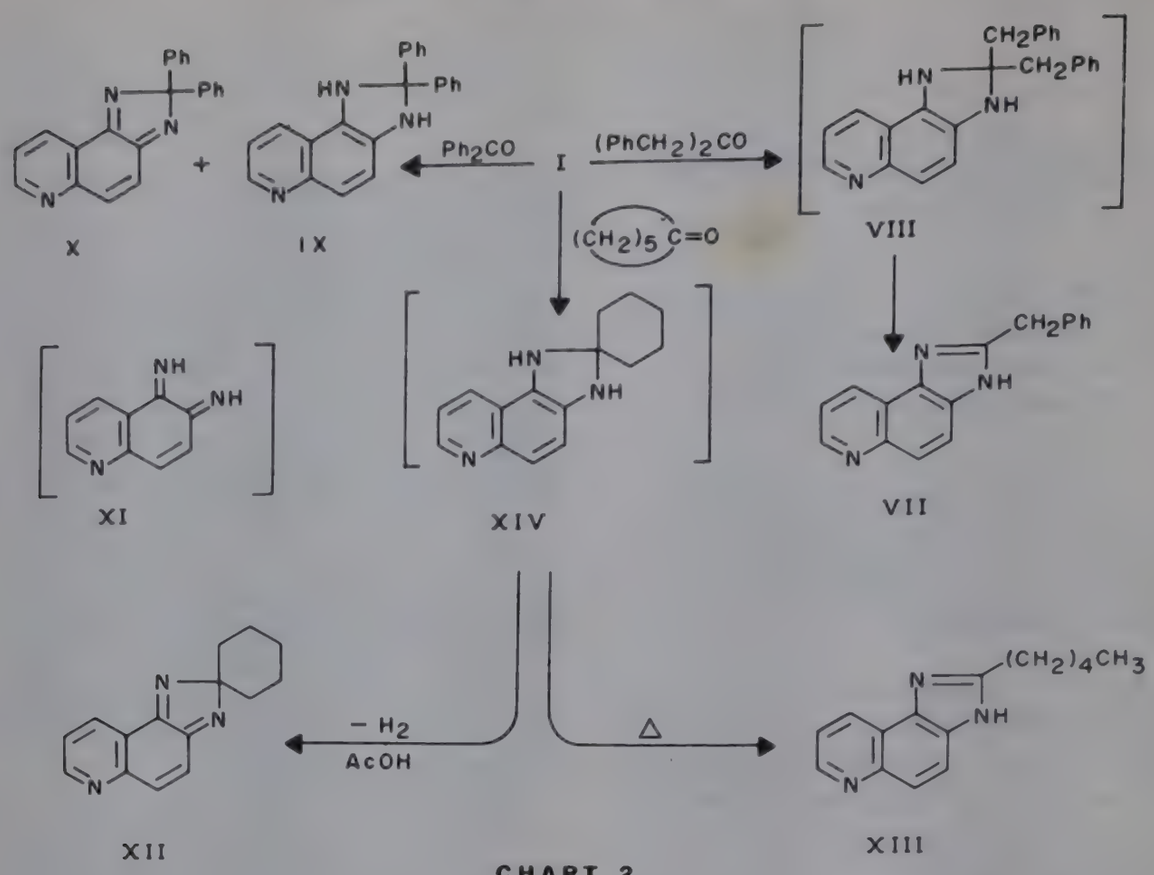


CHART 2

ketone to yield 2-benzylbenzimidazole through 2,2-dibenzyl-2,3-dihydrobenzimidazole. The diazepine derivative is not formed here, although an active methylene group is present, possibly due to the steric hindrance exerted by the two bulky benzyl groups in the formation of dianil, a key intermediate.

A mixture of I and benzophenone on heating in the absence of a solvent yielded two crystalline products (VII, m.p. 120°) and (VIII, m.p. 210°). The structures of VII and VIII were assigned based on spectral and analytical data. The reaction of I with benzophenone in diphenyl ether under reflux exclusively afforded VII. The compound VII may be formed by condensation of I with ketone and VII may be formed by dehydrogenation of VII. However, VII when heated alone at 280° for 6 hr or treated with oxidizing agents like MnO_2 and DDQ did not yield VIII. Thus, the formation of VIII may be explained by the condensation of diimine (IX) formed under reaction conditions, with benzophenone (Chart 2).

I on reaction with acetylacetone in acetic acid medium at room temperature or under thermal conditions in the absence of any solvent yielded 2-methyl-3*H*-imidazo[4,5-*f*]quinoline[3].

Cyclohexane on reaction with I at room temperature in methanol or acetic acid medium yielded spiro[cyclohexane-1,2′-[2*H*]-imidazo[4,5-*f*]-quinoline] (X) as a crystalline solid. However, the reaction of I with cyclohexanone under reflux resulted in the formation of 2-*n*-pentyl-3*H*-imidazo[4,5-*f*]quinoline[3] (XI), identical (m.p., m.m.p. and co-IR) with an authentic sample prepared by the condensation of I and *n*-caproic acid in 4*N* HCl under refluxing conditions[3].

The mechanism of formation of X and XI is shown in Chart 2. This finds support from the reaction of benzene-1,2-diamine with cyclohexanone in the presence of mild oxidising agents to yield dehydrogenated spirocyclohexanobenzimidazole[8] and under reflux 2-*n*-pentylbenzimidazole[6] respectively.

Condensation of quinoline-5,6-diamine (I) with ketones: General procedure

To a solution of I (0.01 mol) in gl. acetic acid (10 ml), appropriate ketone (0.02 mol) was added with shaking and left for 4 hr. The reaction mixture on pouring into cold water and neutralisation with aq. ammonia yielded a gummy material which was filtered through a column of neutral alumina. Benzene-ethyl acetate (9 : 1) eluate gave 2,2,4-trialkyl/aryl-2,3-dihydro[1,4]diazepino[2,3-*f*]quinoline (II) or imidazo-[4,5-*f*]quinolines (VI, X) depending on the nature of ketone. The physical and spectral data of these compounds are given in Table 1.

Reaction of I with benzophenone

A mixture of I (0.01 mol) and benzophenone (0.01 mol) was heated at 220° for 4 hr. The resulting black

Table 1 – Characterisation Data of Diazepino- and Imidazo-quinolines

Compd.	m.p. °C	% Yield	IR νcm^{-1}	PMR ($CDCl_3$) δ ppm	Mol. formula (M^+)	N(%) Calc.	N(%) Found
IIa	—	—	3400(>NH) 1675(−C=N)	1.1 (*t*, 3H, $-CH_2-CH_3$), 1.5 (*s*, *t*-merged, 6H, $-CH_3$, $-CH_2-CH_3$), 1.75 (*q*, 2H, $-N=CH_2-CH_3$), 3.5 (*b*, 1H, NH, D_2O exchangeable), 7-8 (*m*, 3H, aromatic), 8.75 (*m*, 2H, ^1H and ^3H of quinoline moiety)	$C_{17}H_{21}N_3$ (267, 25%)	15.73	—
IIb	—	—	3380(−NH) 1670(−C=N)	—	$C_{19}H_{25}N_3$	14.23	—
IIc	—	—	3360(>NH) 1655(C=N)	—	$C_{19}H_{25}N_3$	14.23	—
IId	—	—	3400(−NH) 1665(−C=N)	—	$C_{21}H_{29}N_3$	13.00	—
IIe	98	25	3350(−NH) 1675(−C=N)	1.8 (*s*, 3H, $-CH_3$), 3.2 (*d*, 2H, $-CH_2-$, *J* = 13 Hz), 4 (*b*, 1H, −NH, D_2O exchangeable), 7-8 (*m*, 13H, aromatic), 8.75 (*m*, ^1H & ^3H of quinoline moiety).	$C_{25}H_{21}N_3$ (363, 4%)	11.57	11.70
IIf	190	20	3250(−NH) 1600(C=N)	1.2 (*b*, 20H, $10\times CH_2-$), 2.8 (*b*, 3H, $-CH_2-C=N$, $-CH-C=N$), 3.8 (*b*, NH, D_2O exchangeable), 7-8 (*m*, 3H, aromatic), 8.75 (*m*, 2H, ^1H and ^3H of quinoline moiety).	$C_{23}H_{29}N_3$ (347, 50%)	12.10	12.15
VI	230	80	3500-3200 (b, −NH)	3.4 (*b*, −NH, D_2O exchangeable) 4.4 (*s*, 2H, $-CH_2Ph$), 7-8 (*m*, 8H, aromatic), 8.75 (*m*, 2H, ^1H & ^3H of quinoline moiety).	$C_{17}H_{13}N_3$ (259, 100%)	16.20	16.30
VII	120	10	3450(−NH)	2.3 (*s*, 2H, 2NH, D_2O exchangeable) 7-8 (*m*, 3H, aromatic), 8.75 (*m*, 2H, ^1H & ^3H of quinoline moiety).	$C_{22}H_{17}N_3$ (323, 12%)	13.00	12.91
VIII	210	10	3000(−CH)	7-8 (*m*, 3H, aromatic), 8.75 (*m*, 2H, ^1H & ^3H of quinoline moiety).	$C_{22}H_{15}N_3$ (321, 10%)	13.08	13.20
X	115	40	—	1.5-2.1 (*b*, 10H, $5\times CH_2-$), 7-8 (*m*, 3H, aromatic), 8.75 (*m*, 2H, ^1H and ^3H of quinoline moiety)	$C_{15}H_{15}N_3$ (237, 100%)	17.72	17.71

IIa-d compounds are low melting solids.
All compounds recrystallised from benzene-ethyl acetate.

mass was eluted through the column of neutral alumina using pet. ether-ethyl acetate (9 : 1) to yield 2,2-diphenyl-2,3-dihydro-1*H*-imidazo[4,5-*f*]quinoline (VII, m.p. 120°C) and 2,2-diphenyl-2*H*-imidazo[4,5-*f*]quinoline (VIII, m.p. 210°)

Reaction of I with acetylacetone

An equimolar mixture of I (0.01 mol) and acetylacetone (0.1 mol) in a minimum amount of gl. acetic acid (10 ml) was left aside overnight. The resinous material which separated on neutralisation eluted through neutral alumina column gave 2-methyl-3*H*-imidazo[4,5-*f*]quinoline[3], m.p. 78° (lit. m.p. 78°). Same compound was obtained when I and acetylacetone were heated under reflux for 3 hr.

Reaction of I with cyclohexanone

A mixture of I (0.5 g) and cyclohexanone (10 ml) was heated under reflux for 4 hr and cooled to room temperature. The mixture was eluted through a column of neutral alumina to yield cyclohexanone in pet. ether eluant and 2-*n*-pentyl-3*H*-imidazo[4,5-*f*]quinoline (XI) as a low melting solid in benzene-ethyl acetate (5 : 1) eluant.

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Reaction of 4-Alkyl/arylthiosemicarbazides with Cyanamide

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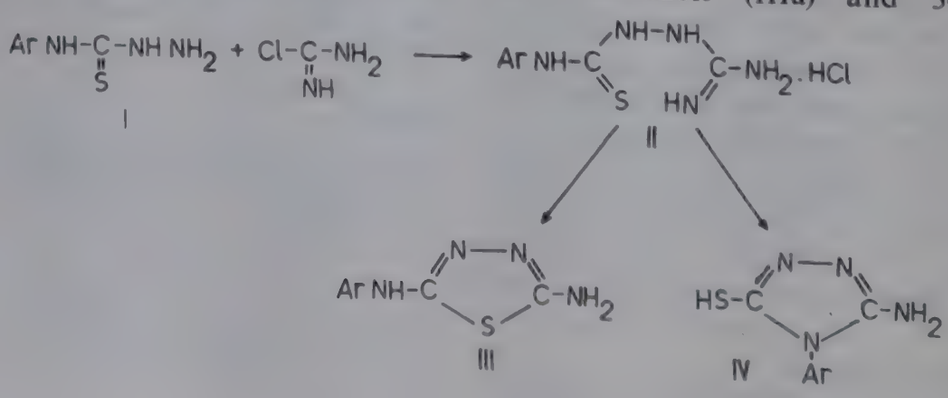
The condensation of cyanamide with 4-alkyl/arylthiosemicarbazide hydrochlorides (I.HCl) results in the formation of 2-alkyl/arylamino-5-amino-1,3,4-thiadiazoles (III) and 3-amino-4-alkyl/aryl-5-mercapto-1,2,4-triazoles (IV).

The chemistry of 1,2,4-triazole and 1,3,4-thiadiazole derivatives continues to draw the attention of synthetic organic chemists due to their varied pharmacological properties[1]. Kurzer and Godvry[2] examined the interaction of 1-aminoguanidine with isothiocyanates and isocyanates and observed that 1-amidino-4-alkyl/aryl(thio)semicarbazide intermediates formed were found to undergo cyclization to 2-alkyl/aryl-amino-5-amino-1,3,4-thiadiazoles in acid media and to 4-substituted-3-amino-5-mercapto-1,2,4-triazoles in the presence of alkali. In the present study the interaction of an equimolar mixture of 4-phenylthiosemicarbazide (Ia) and cyanamide was first attempted at water-bath temperature in the absence of a solvent and a catalyst. Even prolonged heating did not afford any condensation product. The condensation reaction also failed in a solvent of high boiling point like butanol. Since cyanamides are known to react with thioureas only in the presence of acid, the reaction of Ia with cyanamide was attempted in the presence of hydrochloric acid when a homogeneous viscous liquid was formed. The reaction mixture after heating for 10 min over a water-bath, was cooled and extracted with water. The water soluble and the water insoluble portions were examined separately. The water soluble portion on neutralization with alkli afforded 2-phenylamino-5-amino-1,3,4-thiadiazole (IIIa; Ar = Ph) whose identity was proved by comparison with an authentic sample[2]. The water insoluble product gave an S-benzyl derivative indicating the presence of an enolisable thioketo grouping in the product and was identified as 3-amino-4-phenyl-5-mercapto-1,2,4-triazole (IVa; Ar = Ph) by comparison with an authentic sample[2]. The reaction was extended to other 4-alkyl/arylthiosemicarbazides and in almost all the cases both III and IV were isolated in varying yields. In certain cases the yield of III was very low, and hence it could not be isolated and characterized.

A plausible mechanism for the formation of III and IV should involve the intermediacy of 1-amidino-4-phenylthiosemicarbazide hydrochloride (II; Scheme 1). As in the reaction of thioureas with cyanamide, here also the formation of a chloroamidine by the addition of HCl to cyanamide is very likely. The chloroamidine so formed could undergo a necleophilic displacement of chlorine by the attack of amino group of the hydrazino nitrogen of I resulting in the formation of the intermediate II. The attack on chloroamidine by the sulphur atom of I could result in the formation of a monosulphide which could undergo a rearrangement involving a 1,3-migration to form II. The possibility for the latter pathway is quite unlikely in the present case, because the monosulphides are known to undergo decomposition under the experimental conditions used here and produce alkyl/aryl isothiocyanate[3]. The nonformation of any alkyl/aryl isothiocyanate in the reaction examined, ruled out this possibility.

It is well known that 1-amidino-4-phenyl-thiosemicarbazide (IIa) undergoes cyclization under acidic conditions to give 5-amino-2-phenylamino-1,3,4-thiadiazole (IIIa) and 3-amino-4-phenyl-5-



Scheme 1

Table 1—Characterization Data of 1,3,4-Thiadiazoles (III) and 1,2,4-Triazoles (IV)

Compd	Ar/R	1,3,4-Thiadiazole (III)				1,2,4-Triazole (IV)			
		Mol. formula	Yield (%)	m.p. C	lit.[2] m.p. °C	Mol. formula	Yield (%)	m.p. °C	lit.[2] m.p. °C
b	*p*-H_3C-C_6H_4	$C_9H_{10}N_4S$	32	206	206	$C_9H_{10}N_4S$	68	280	280
c	*p*-Cl-C_6H_4	—				$C_8H_7N_4ClS$	85	292	290
d	*p*-MeO-C_6H_4	—				$C_9H_{10}N_4SO$	75	262	259
e	*p*-C_2H_5O-C_6H_4	$C_{10}H_{12}N_4SO$	35	224		$C_{10}H_{12}N_4SO$	65	226	—
f	Me	—				$C_3H_6N_4S$	80	270	269
g	Et	$C_4H_8N_4S$	38	208		$C_4H_8N_4S$	62	206	—
h	*n*-Pr	—				$C_5H_{10}N_4S$	85	160	—
i	*i*-Pr	$C_5H_{10}N_4S$	36	210		$C_5H_{10}N_4S$	64	194	191
j	*n*-Bu	$C_6H_{12}N_4S$	40	115		$C_6H_{12}N_4S$	60	154	153

mercapto-1,2,4-triazole (IVa) under alkaline condition. But in the present experiment it has been observed that both the products are formed under acidic condition. The formation of both of these products could be explained by the nucleophilic displacement of ammonia from the intermediate II either by the attack of the sulphur or the nitrogen atom carrying the alkyl/aryl substituent, resulting in the formation of 1,3,4-thiadiazole and 1,2,4-triazole respectively. The postulated intermediate II however, could not be isolated.

The present reaction appears to be a more convenient method for the preparation of 1,3,4-thiadiazole and 1,2,4-triazole derivatives, as the yield of both the products are better than those reported already and also because the products are formed under the same conditions and are easily separable.

The purity of the products in each case was ascertained by TLC. All melting points reported are uncorrected. Satisfactory elemental analyses were obtained for all the compounds reported herein.

Reaction of 4-phenylthiosemicarbazide hydrochloride (Ia) with cyanamide: Formation of 2-amino-5-phenylamino-1,3,4-thiadiazole (IIIa) and 3-amino-5-mercapto-4-phenyl-1,2,4-triazole (IVa)

In a typical experiment an intimate mixture of Ia.HCl (1.52 g, 0.01 mol) [or Ia and conc. HCl (1 ml)] and cyanamide (0.42 g, 0.01 mol) was heated on a boiling water-bath for about 10 min. A vigorous exothermic reaction was found to occur and the resultant homogeneous syrupy liquid solidified within minutes. The solid thus obtained was finally powdered and extracted with cold water. The water extracts on basification afforded 2-phenylamino-5-amino-1,3-4-thiadiazole (IIIa), yield 0.6 g (30%), m.p. 206° (EtOH, as shining needles) (lit.[2], m.p. 206°). The water insoluble portion on extraction with dil. alkali and neutralization of the alkaline extract yielded 3-amino-4-phenyl-5-mercapto-1,2,4-triazole (IVa) as shining needles (yield 1.3 g, 70%) m.p. 268° (lit.[2], m.p. 266°).

The characterization data of other 1,3,4-thiadiazoles (III) and 1,2,4-triazoles (IV) are given in Table 1.

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Reaction of Chalcone with Sulphur

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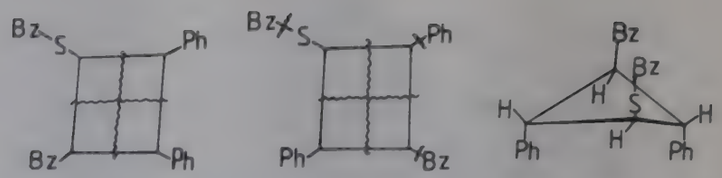
trans, *trans*, *trans*-2-Benzoyl-2-benzoylthio-1, 3-diphenylcyclobutane (III) is obtained, in low yield, by the thermolytic reaction of chalcone with sulphur.

In a previous communication we reported[1] the formation of 2, 4, 5-triphenylthiophene (TPT) in the thermolytic reaction (180-200°) of chalcone with sulphur. In the present report we describe the isolation of a cyclobutane derivative (A) when the above reaction is carried out at 200° for 3 hr in N_2-atmosphere.

The compound-A crystallises from acetone, m.p. 218-20°. In the mass spectrum M^+ appears at *m/z* 448. The intensity of (M+2) ion peak is indicative of the presence of one sulphur atom in the molecule[2], in confirmity with the molecular formula $C_{30}H_{24}O_2S$. Its molecular weight (448) suggests that two chalcone moieties and one sulphur atom are involved in its formation.

The IR spectrum of (A) in KBr shows bands at 1690 cm^{-1} (Ar−CO−)[3] and 1670, 1200, 1190, 1160, 1030, 990, 940 and 930 (−O−S−)[4]. The IR bands
‖
C
located at 3095, 3065, 3040, 1605, 1590, 1500, 770, 740, 705 and 700 cm^{-1} suggest the presence of mono-substituted phenyl group(s). The prominent bands at 2900 and 2860 together with a sharp band at 1010 cm^{-1} provide good evidence for the presence of methine protons of a cyclobutane ring[5].

The proof for the presence of a benzoyl group in the molecule is provided by the peak at *m/z* 105 in the mass spectrum. The 60 MHz PMR spectrum of (A) in $CDCl_3$ displays a two-proton multiplet at τ 2.15 and points to the presence of only one benzoyl substituent. A broad multiplet (18H) centred at τ 2.75 has been assigned to aromatic protons. Besides, there are two sets of multiplets centred at τ 5.35 (2H) and 4.95 (2H), which can be assigned to the cyclobutane methine protons. The upfield signal located at τ 5.35 is apparently due to cycloalkane protons to which two phenyl groups are attached, while the downfield multiplet at τ 4.95 presumably arises due to cyclobutane methine protons bearing the electron withdrawing substituents, viz. benzoyl and thioester groups.



(I) (II) (III)

Ph = phenyl Bz = benzoyl

Based on the above facts two alternative structures (I or II) can be proposed for the compound-A. Its mass spectrum shows two principal fragments, viz. *m/z* 240 and 208, which arise due to the cleavage of cyclobutane ring[6], as depicted in structure (II). The other mass peak at *m/z* 343 can be assigned to the fragment[7] ion, $Ph_2BzC_4H_4S^+$. The conspicuous absence of peak at *m/z* 180, corresponding to fragment ion $(PhCHCHPh)^+$, rules out structure (I) for compound-A.

On the basis of the aforesaid evidences we conclude that compound-A is 2-benzoyl-4-benzoylthio-1, 3-diphenylcyclobutane (III), and tentatively assign *trans*, *trans*, *trans* stereochemistry to the molecule.

Equimolar quantities of chalcone and sulphur were heated at 200° (oil-bath) for 3 hr, under N_2-atmosphere. The reaction mixture was chromatographed (SiO_2) and elution of the column with benzene furnished the cyclobutane derivative (~0.5%), which recrystallised from acetone, m.p. 218-20° (uncorr.). TLC(SiO_2) R_f, 0.19 (cf. R_f(TPT), 0.83); solvent system: benzene-pet. ether (40-60°) (1:1) (Found: C, 80.0; H, 5.2. $C_{30}H_{24}O_2S$ requires C, 80.4; H, 5.4%). Mass spectrum: *m/z* [70 eV], Relative intensity (%), M^+ 448 (8.02), 343 (3.0), 240 (15.0), 208 (25.1), 105 (100.0), 91 (5.0), and 77 (25.0).

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Reaction of Sulphuryl Chloride with Some Schiff Bases

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The reaction of sulphuryl chloride with schiff bases has been studied. In each case, pure crystalline products have been isolated, and their structures elucidated on the basis of IR, PMR and mass spectral data. A plausible mechanism is advanced for the formation of observed products.

As of today the Ritter reaction has emerged as a very important synthetic reaction[1-8]. Chloramination of olefins can be achieved by a modified Ritter reaction using sulphuryl chloride in acetonitrile[9]. This prompted us to investigate the reaction of this reagent with various schiff bases (**1a-r**).

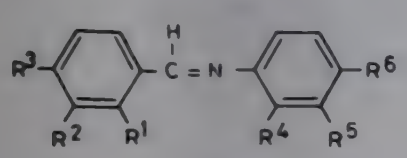
Sulphuryl chloride in acetonitrile reacted smoothly with schiff bases (**1a-c**) giving rise to the corresponding benzaldehyde phenylhydrazones (**8a-c**). Reaction of **1d-m** with sulphuryl chloride in acetonitrile yielded the corresponding N-phenylbenzimidines (**10d-m**). Here the chloronium ion formed by the addition of chlorine to the C=N double bond of a schiff base is attacked by the nitrile function, leading to the generation of imidoyl chloride (**3**), which gets readily hydrolysed by adding water to give the corresponding amine. The amine (**6**) leads to the formation of two products, viz. N-phenylbenzimidines and benzaldehyde phenylhydrazones. The latter compounds are formed via the corresponding diaziridine intermediates (Scheme 1).

8a exhibited IR absorptions at 3300 (νNH) and 1600 (νC=N). It displayed PMR signals at δ 4.9 (*s*, 1H, NH), 6.4-7.4 (*m*, 9H, aromatic + 1H, CH, olefinic). **10d** exhibited IR absorption bands at 3360, 3480 (νNH), 1615, 1590 (νC=N), 1470, 1320, 1110, 840, 750 cm^{-1}. It displayed PMR signals at δ 5.0 (*s*, 1H, NH), 6.5-7.7 (*m*, 9H, aromatic + 1H, NH, exchangeable with(D_2O).

Reaction of Schiff bases (**1n-r**) with sulphuryl chloride in acetonitrile gave rise to the corresponding benzanilides (**13n-r**) (Scheme 2). Apparently(the nitrile function does not participate in the reaction. **13a** exhibited IR absorption maxima at 3250 (νNH), 1670 (νC=O), 1590, 1510 (νC=N) cm^{-1}. It displayed PMR signals at δ 3.9 (*d*, 3H, OCH_3), 6.8-7.4 (*m*, 8H, aromatic + 1H, NH, exchangeable with D_2O).

The characterisation data of all the products obtained (yield, m.p., and analytical data) are listed in Table 1.

All the melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus. The IR spectra were recorded on Perkin-Elmer model-580 spectrophotometer and PMR spectra on a Varian EM-390 (90 MHz) instrument; chemical shifts are expressed in δ-scale downfield from TMS internal reference. Mass spectra were recorded on a Jeol-300D mass spectrometer at 70 eV.



1 a-m

a : R^3 = Br, R^1 = R^2 = R^4 = R^5 = R^6 = H

b : R^3 = R^6 = Cl, R^1 = R^2 = R^4 = R^5 = H

c : R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H

d : R^3 = Cl, R^1 = R^2 = R^4 = R^5 = R^6 = H

e : R^6 = Cl, R^1 = R^2 = R^3 = R^4 = R^5 = H

f : R^6 = NO_2, R^1 = R^2 = R^3 = R^4 = R^5 = H

g : R^3 = R^6 = NO_2, R^1 = R^2 = R^3 = R^4 = H

h : R^3 = R^5 = NO_2, R^1 = R^2 = R^4 = R^6 = H

i : R^3 = R^4 = NO_2, R^1 = R^2 = R^5 = R^6 = H

j : R^5 = NO_2, R^1 = R^2 = R^3 = R^4 = R^6 = H

k : R^4 = NO_2, R^1 = R^2 = R^3 = R^5 = R^6 = H

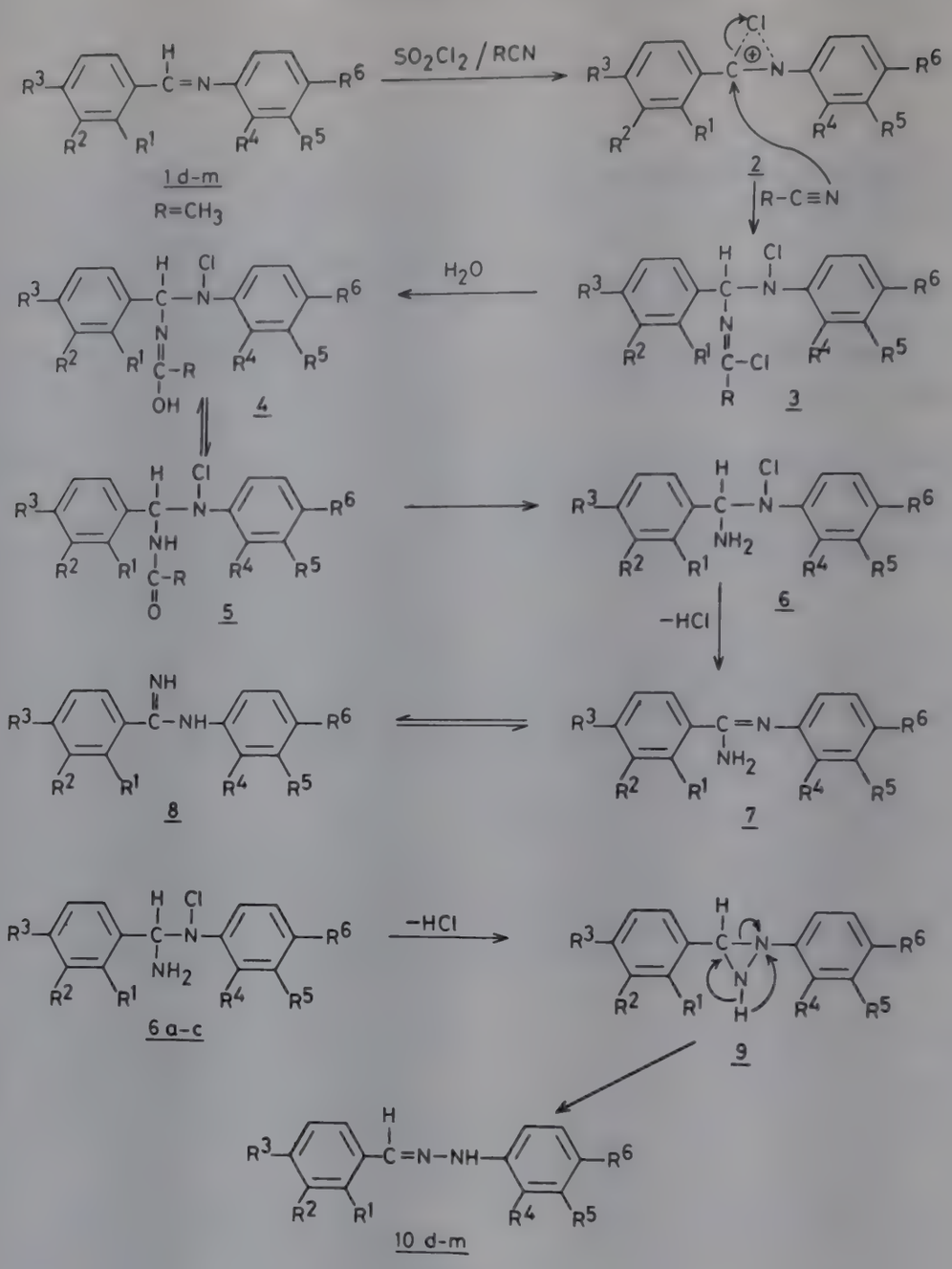
l : R^3 = Br, R^6 = NO_2, R^1 = R^2 = R^3 = R^4 = H

m : R^2 R^3 = OCH_3, R^5 = NO_2, R^1 = R^4 = R^6 = H

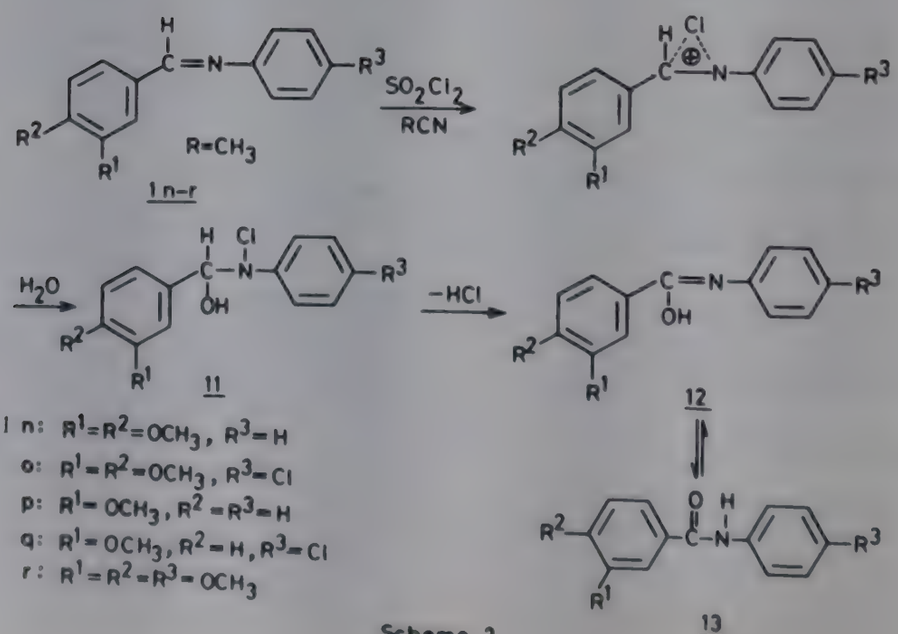
General procedure

Sulphuryl chloride (0.18 ml, 0.005 mol) in dry CH_3CN (5 ml) was added dropwise during 5 min to a stirred solution of schiff base (**1d**, 0.005 mol) in CH_3CN (10 ml) at 0°. After 10 min the mixture was diluted with water, stirred at room temperature for additional 20 min and extracted with CH_2Cl_2 (3 × 2 ml). The organic layer was washed with water, dried (Na_2SO_4), the solvent evaporated, and residue purified by crystallization from ethinol to furnish **8d**.

We wish to thank the authorities of Indian Institute of Technology, Kanpur for providing financial assistance to one of us (SRG).



Scheme 1



1 n: $R^1=R^2=OCH_3$, $R^3=H$
o: $R^1=R^2=OCH_3$, $R^3=Cl$
p: $R^1=OCH_3$, $R^2=R^3=H$
q: $R^1=OCH_3$, $R^2=H$, $R^3=Cl$
r: $R^1=R^2=R^3=OCH_3$

Scheme 2

Table 1 – Characterisation Data of Products of Reaction of Schiff Bases with Sulphuryl Chloride

Product	Yield (%)	m.p. (lit. m.p.)	Mol. formula	Found (%) (calc)		
				C	H	N
8a	71	169-70 (170°)	$C_{13}H_{11}BrN_2$	56.7 (56.1)	4.0 (3.9)	10.2 (9.7)
8b	65	112-13°	$C_{13}H_9Cl_2N_2$	59.3 (58.8)	3.4 (4.0)	10.7 (9.7)
8c	71	157-58 (160°)	$C_{13}H_{12}N_2$	79.6 (80.0)	6.1 (7.8)	14.3 (13.4)
10d	65	115-16°	$C_{13}H_{11}ClN_2$	67.8 (67.4)	4.8 (4.1)	12.2 (13.1)
10e	51	120-21°	$C_{13}H_{11}N_2Cl$	67.8 (66.8)	4.8 (4.2)	12.1 (11.6)
10f	65	172-73°	$C_{13}H_{11}N_3O_2$	64.7 (64.5)	4.6 (4.0)	17.4 (17.1)
10g	68	194-95°	$C_{13}H_{10}N_4O_4$	54.5 (54.1)	3.5 (3.6)	19.6 (18.9)
10h	64	196-97°	$C_{13}H_{10}N_4O_4$	54.5 (54.3)	3.5 (3.8)	19.6 (20.0)
10i	67	88-89°	$C_{13}H_{10}N_4O_4$	54.5 (54.1)	3.5 (3.1)	19.6 (20.5)
10j	62	105-06°	$C_{13}H_{11}N_3O_2$	64.7 (64.1)	4.6 (4.2)	17.4 (17.1)
10k	69	95-96°	$C_{13}H_{11}N_3O_2$	64.7 (64.1)	4.6 (3.6)	17.4 (16.9)
10l	60	155-56°	$C_{13}H_{10}BrN_3O_2$	48.8 (48.1)	3.1 (3.5)	13.1 (12.6)
10m	65	175-76°	$C_{15}H_{15}N_3O_4$	59.8 (58.7)	5.0 (4.1)	14.0 (13.1)
13n	64	141-42°	$C_{15}H_{15}O_3N$	69.5 (70.1)	5.8 (4.8)	5.4 (4.9)
13o	65	124-25°	$C_{13}H_{14}ClNO_3$	61.9 (61.0)	4.8 (4.1)	4.2 (4.1)
13p	64	148-49°	$C_{14}H_{13}NO_2$	74.0 (73.6)	5.7 (5.1)	6.2 (6.0)
13q	65	155-56°	$C_{14}H_{12}ClNO_2$	64.4 (64.1)	4.6 (4.1)	5.4 (5.0)
13r	63	112-13°	$C_{16}H_{17}NO_4$	66.9 (66.1)	5.9 (5.1)	4.9 (4.1)

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Preparation & Deamination of Methyl N-Alkyl-3-fattyaziridine-2-carboxylates

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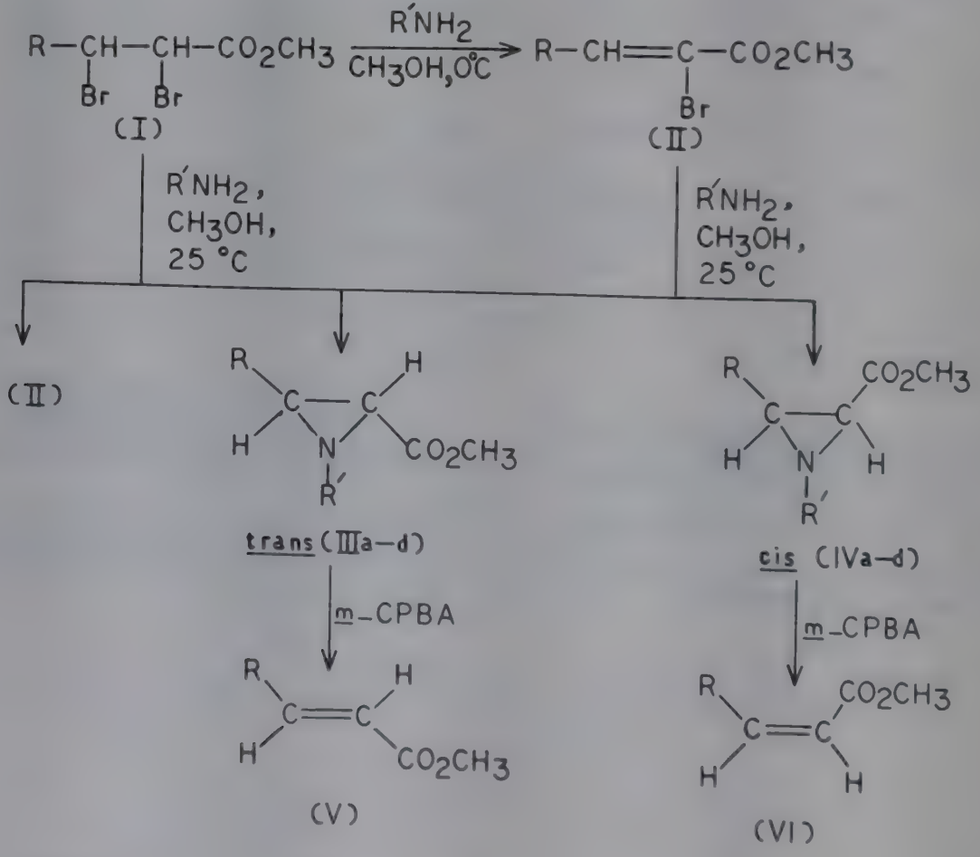
Methyl 2,3-dibromohexadecanoate on treatment with primary amines ($R-NH_2$; $R=CH_3$, C_2H_5, C_4H_9 and $C_6H_5CH_2$) affords a mixture of methyl N-alkyl-*trans*/*cis*-2,3-epiminohexadecanoates (III/IV). The *trans*-epimino derivatives (III) on deamination with *m*-chloroperbenzoic acid furnish the *trans*-alkenoates (V). The *cis*-epimino derivatives (IV) on similar treatment give the *cis*-alkenoates (VI).

Several aziridine derivatives have been used as insect chemosterilents, antimicrobials and as important pharmaceuticals[1-3]. These aziridines were prepared by the reaction of short chain α,β-dihalogencarbonyl compounds with amines[4]. The application of this method in fatty acid chemistry was not exploited because of the inaccessibility of the required starting materials. In our earlier communications[5,6] we reported the preparation of 3-fattyaziridines using ammonia and N-aminophthalimide as reagents. In this note the preparation of N-alkyl-3-fattyaziridines and their reaction with *m*-chloroperbenzoic acid (*m*-CPBA) are described.

Treatment of methyl 2,3-dibromohexadecanoate (I) with primary amines (methyl, ethyl, butyl or benzylamine) at 25° gave a readily separable mixture (~1:1) of the *trans*- and *cis*-N-alkyl-2,3-epimino derivatives (IIIa-d, IVa-d) along with a minor amount of ene bromide (II) (Scheme 1). The spectral data of epimino derivatives are given in Table 1. The special features of the spectra are discussed below:

The PMR spectra exhibited characteristic signals at δ 2.2-2.3 and 1.9-2.19 due to methine protons at C-2 and C-3 respectively of *trans*-epimino derivatives (IIIa-d). However, in the case of *cis*-epimino derivatives (IVa-d) these methine protons resonated at δ 1.88-2.08 and 1.60-1.78. The ring protons *cis* to the N-alkyl bond appeared higher field than the corresponding *trans*-



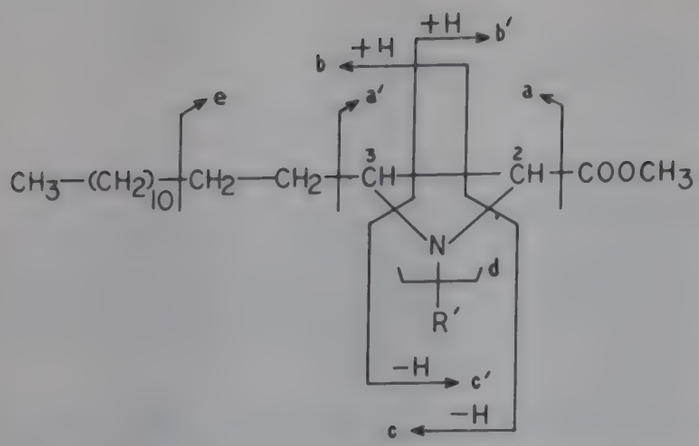
$R=CH_3(CH_2)_{12}$; $R'=CH_3$ (IIIa, IVa); C_2H_5 (IIIb, IVb); C_4H_9 (IIIc, IVc); $C_6H_5CH_2$ (IIId, IVd).

Scheme 1

Table 1—Characterization Data of *trans*-(III) and *cis*-Epimines (IV)

Compd	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.) C	H	N	IR[a] (cm^{-1})	PMR (δ, ppm)
IIIa*	48	Semi-solid	$C_{18}H_{35}NO_2$	72.6 (72.7	11.8 11.9	4.6 4.7)	(CCl_4): 3020 (C−H, ring), 1735 (*COO*CH_3), 1340 (C−N−C), 1180, 1060, 1040 (C−O).	(CCl_4): 3.66 (*s*, 3H, $-CO_2CH_3$), 2.49 (*s*, 3H, N−CH_3), 2.2 (*d*, 1H, C_2-H, J=2 Hz), 1.9 (*m*, 1H, C_3-H), 1.3 (br, *s*, 24H, chain-CH_2), 0.88 (*t*, 3H, CH_3).
IIIb†	49	Liquid	$C_{19}H_{37}NO_2$	73.2 (73.3	11.9 12.0	4.4 4.5)	(CCl_4): 3020, 1735, 1350, 1195, 1070, 1040.	(CCl_4): 3.65 (*s*, 3H, $-CO_2CH_3$), 2.68 (*q*, 2H, N−CH_2−, J=7 Hz), 2.22 (*d*, 1H, C_2-H, J=2 Hz), 2.0 (*m*, 1H, C_3-H), 1.3 (br *s*, 24H, chain-CH_2), 1.1 and 0.88 (*t*, each merged partly, 6H, CH_2-CH_3 and terminal CH_3).
IIIc‡	50	Liquid	$C_{21}H_{41}NO_2$	74.2 (74.3	12.0 12.2	4.0 4.1)	(CCl_4): 3020, 1735, 1340, 1180, 1070, 1030.	(CCl_4): 3.68 (*s*, 3H, $-CO_2CH_3$), 2.65 (overlapped *t*, 2H, N−CH_2−), 2.22 (*d*, 1H, C_2-H, J=2.5 Hz), 1.98 (*m*, 1H, C_3-H), 1.5 and 1.3 (br *s*, 28H, N−$CH_2(CH_2)_2$ and chain-CH_2), 1.07 and 0.87 (*t*, each merged partly, 6H, $-CH_2CH_3$ and terminal CH_3).
IIId**	50	44-45	$C_{24}H_{39}NO_2$	77.1 (77.2	10.4 10.5	3.7 3.8)	(CCl_4): 3600 (C−H, aromatic), 3020 (C−H, ring), 1730,1350,1175,1070, 1025, 725 and 690.	($CDCl_3$): 7.2 (*m*, 5H, Ar-*H*), 3.82 (*hump*, 2H, $-CH_2-C_6H_5$), 3.66 (*s*, 3H, $-CO_2CH_3$), 2.3 (unresolved *d*, 1H, C_2-H), 2.19 (*m*, 1H, C_3-H), 1.23 (br *s*, 24H, chain-CH_2) and 0.88 (*t*, 3H, CH_3).
IVa	44	45-46	$C_{18}H_{35}NO_2$	72.6 (72.7	11.8 11.9	4.6 4.7)	(CCl_4): 3015 (C−H, ring), 1735 (*COO*CH_3), 1380 (C−N−C), 1175, 1030 (C−O).	(CCl_4): 3.67 (*s*, 3H, $-CO_2CH_3$), 2.38 (*s*, (C3H, N−CH_3), 1.88 (*d*, 1H, C_2-H, J =5 Hz), 1.65 (*m*, 1H, C_3-H), 1.25 (br *s*, 24H, chain-CH_2), 0.88 (*t*, 3H, CH_3).
IVb	44	33-34	$C_{19}H_{37}NO_2$	73.2 (73.3	11.9 12.0	4.3 4.5)	(CCl_4): 3015, 1740, 1355, 1170, 1097, 1030.	(CCl_4): 3.68 (*s*, 3H, $-CO_2CH_3$), 2.3 (*q*, 2H, N−CH_2, J=7 Hz), 1.9 (*d*, 1H, C_2-H, J =6 Hz), 1.6 (*m*, 1H, C_3-H), 1.3 (br, *s*, 24H, chain-CH_2), 1.1 and 0.88 (*t*, each merged partly, 6H, CH_2-CH_3 and terminal CH_3).
IVc	46	29.30	$C_{21}H_{41}NO_2$	74.1 (74.3	12.0 12.2	4.0 4.0)	(CCl_4): 3020, 1740, 1370, 1175, 1030.	(CCl_4): 3.66 (*s*, 3H, $-CO_2CH_3$), 2.28 (overlapped *t*, 2H, N−CH_2−), 1.9 (*d*, 1H, C_2-H, J=7 Hz), 1.6 (*m*, 1H, C_3-H), 1.5 and 1.3 (br *s*, 28H, N−$CH_2-(CH_2)_2$ and chain-CH_2), 1.05 and 0.88 (two deformed *t* merged together, 6H, $-CH_2CH_3$ and terminal CH_3).
IVd	46	54-55	$C_{24}H_{39}NO_2$	77.1 (77.2	10.5 10.5	3.7 3.8)	(CCl_4): 3060, 3020, 1735, 1380, 1185, 1070, 760, 740, 700.	($CDCl_3$): 7.27 (*m*, 5H, Ar-*H*), 3.66 (*s*, 3H, $-CO_2CH_3$), 3.48 (*dd*, 2H, $CH_2-C_6H_5$, J =10 Hz and 7 Hz), 2.08 (*d*, 1H, C_2-H, J =6.2 Hz), 1.78 (*m*, 1H, C_3-H), 1.24 (br *s*, 24H) and 0.88 (*t*, 3H, CH_3).

*MS: *m/z* 297 (M^+, 0.7%), 282 (**d**, 4), 238 (**a**, 85), 226 (**b**, 2), 224 (**c**, 3), 142 (**e**, 100), 114 (**a′**, 8), 102 (**b′**, 2), 100 (**c′**, 2).
†MS: *m/z* 331 (M^+, 0.7%), 282 (**d**, 3), 252 (**a**, 89), 240 (**b**, 4), 238 (**c**, 4), 156 (**e**, 100), 128 (**a′**, 10), 116 (**b′**, 16), 114 (**c′**, 3).
‡MS: *m/z* 339 (M^+, 0.4%), 282 (**d**, 9), 280 (**a**, 100), 268 (**b**, 4), 266 (**c**, 4), 184 (**e**, 96), 156 (**a′**, 98), 144 (**b′**, 10), 142 (**c′**, 15).
MS: *m/z* 373 (M^+, 2.7%), 282 (d**, 12), 314 (**a**, 25), 302 (**b**, 2), 300 (**c**, 4), 190 (**a′**, 9), 178 (**b′**, 0.5), 176 (**c′**, 0.6), 146 (178 − 32, 20), 132 (CH_2=N(CH)=CH_2), $-CH_2C_6H_5$, 7), 91 ($C_6H_5\overset{+}{C}H_2$, 100).



protons. This is in agreement with the finding of Brois[7] for N-alkylaziridines. The coupling constant[8] for *trans*-isomers (J = 2-2.7 Hz) was lower than that for *cis*-isomers (J = 6.2-7 Hz). The coupling constants between C-2 and C-3 protons indicated that epimino derivatives III and IV had *trans*- and *cis*-geometry, respectively.

The mass spectra of all the N-alkylepimines exhibited molecular ions along with (M + 1) ions. Formation of the diagnostic ions **a** and **a'** require α-cleavage on either side of the aziridine ring (Fig. 1). In addition to the usual fatty ester peaks, the transannular fragmentation also occurred with concomitant hydrogen transfer to give the ions **b** and **b'**. In general, the intensity differences were small between the peaks of *cis*- and *trans*-isomers.

The reaction of I and primary amines in equimolar amounts at 0° gave only methyl 2-bromohexadec-2-enoate (II) as the sole product which had identical spectral data (IR, PMR) and TLC mobility with an authentic sample prepared earlier[5]. Compound II on further reaction with primary amines afforded *trans*-(IIIa-d) and *cis*-epimines (IVa-d). The characterization data of the resulting epimines were identical with those of the epimines obtained directly from I.

Formation of *trans*- and *cis*-epimines was also confirmed by deamination[9] of epimines by *m*-CPBA. The *trans*-epimines (IIIa-d) on treatment with *m*-CPBA gave methyl hexadec-*trans*-2-enoate (V), while *cis*-epimines furnished methyl hexadec-*cis*-2-enoate (VI). The compounds V and VI showed similar chromatographic and spectral (IR, PMR) characteristics as reported by Gunstone and Ismail[10]. The deamination of aziridines is a stereospecific reaction. *m*-CPBA deamination is probably arise via N-oxide intermediate[9].

All melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP3-100 spectrometer (ν_{max} in cm^{-1}), PMR spectra on a Varian A60 spectrometer using TMS as internal standard (chemical shifts in δ, ppm), and mass spectra on a JEOL JMS D300 spectrometer. Methyl 2,3-dibromohexadecanoate (I) was prepared from methyl hexadec-*trans*-2-enoate as described earlier[5].

Epimino derivatives from methyl 2,3-dibromohexadecanoate (I); General procedures

(a) To a well stirred solution of I (0.005 mol) in methanol (15 ml) was added an appropriate primary amine [ethyl-, butyl- or benzyl-amine (0.02 mol) or methylamine (1.5 ml, 40%)] and the reaction mixture stirred at room temperature (~25°). The progress of the reaction was monitored by TLC. After the reaction was over (reaction period for ethyl- and butyl-amines 12 hr and for benzylamine 18 hr), methanol was evaporated under reduced pressure and the residue extracted with ethyl ether. The ethereal extract was washed with 3% HCl and water, dried (anhyd. sodium sulphate) and solvent removed under reduced pressure. The residual crude product was subjected to column chromatography, using pet. ether with increasing amount of diethyl ether as eluent to afford one minor (II) and two major (III and IV) products. The yield, elemental analysis and spectral data of the products are given in Table 1.

(b) The compound I (0.005 mol) in methanol (15 ml) was stirred with an equivalent amount of a primary amine in methanol (10 ml) at 0° for 24 hr. After similar work-up as above with diethyl ether, methyl 2-bromohexadec-2-enoate (II, ~93%) was obtained. (Found: C, 58.7; H, 8.9. $C_{17}H_{31}O_2Br$ requires C, 58.8; H, 9.0%); IR (CCl_4): 1725, 1715 (ester CO), 1610 (C=C) and 645 (C-Br); PMR (CCl_4): 6.61 (t, 1H, $-CH=C-CO_2CH_3$, J = 8 Hz), 3.78 (s, 3H, CO_2CH_3), 2.5 (m, 2H, $-CH_2-CH=C-$), 1.3 (br, s, 22H, chain CH_2) and 0.88 (t, 3H, terminal CH_3). The compound II on further treatment with a primary amine gave *trans*- and *cis*-epimino derivatives.

Deamination of epimines

trans-Epimino compounds (IIIa-d, 0.002 mol each) and an equivalent amount of *m*-CPBA in benzene (10 ml) were kept in dark at 25° for 4 hr. The reaction mixture was then extracted with benzene, the extract washed with aq. sodium carbonate, dried (sodium sulphate), and solvent removed *in vacuo*, The liquid product thus obtained was subjected to column chromatography over silica gel. Elution with pet. ether gave methyl hexadec-*trans*-2-enoate (V) in ~85% yield; IR (neat): 1730 (ester CO), 1650 (C=C), 980 (*trans*-olefin); PMR (CCl_4): 6.9 (dd, 1H, proton β to ester carbonyl, J = 15 Hz), 2.6 (m, 2H, $-CH_2CH=CH-$). A similar peracid treatment of *cis*-epimines (IVa-d) gave methyl hexadec-*cis*-2-enoate ~90% yield; IR (neat): 1725, 1640, 820 (*cis*-olefin); PMR (CCl_4): 6.25 and 6.08 (each t, overlapping, 1H, C_3-H), 5.68 (d, 1H, C_2-H, J = 10 Hz).

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One-step Synthesis of 3,3′-Benzylidene-bis(4-hydroxy-1-methyl/phenyl-2-quinolones)

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A one-step synthesis of 3,3′-benzylidenebis(4-hydroxy-1-methyl/phenyl-2-quinolones) (**5**) involves the condensation of 4-hydroxy-1-methyl/phenyl-2-quinolone (**1**) with benzylideneanilines in acetic acid. The structure of the products have been established on the basis of spectral data.

4-Hydroxy-2-quinolone derivatives are known to exhibit a variety of physiological activities[1-7]. It was therefore considered worthwhile to synthesise 3,3′-benzylidenebis(4-hydroxy-1-methyl/-phenyl-2-quinolones) (**5**) and to evaluate them for their physiological properties.

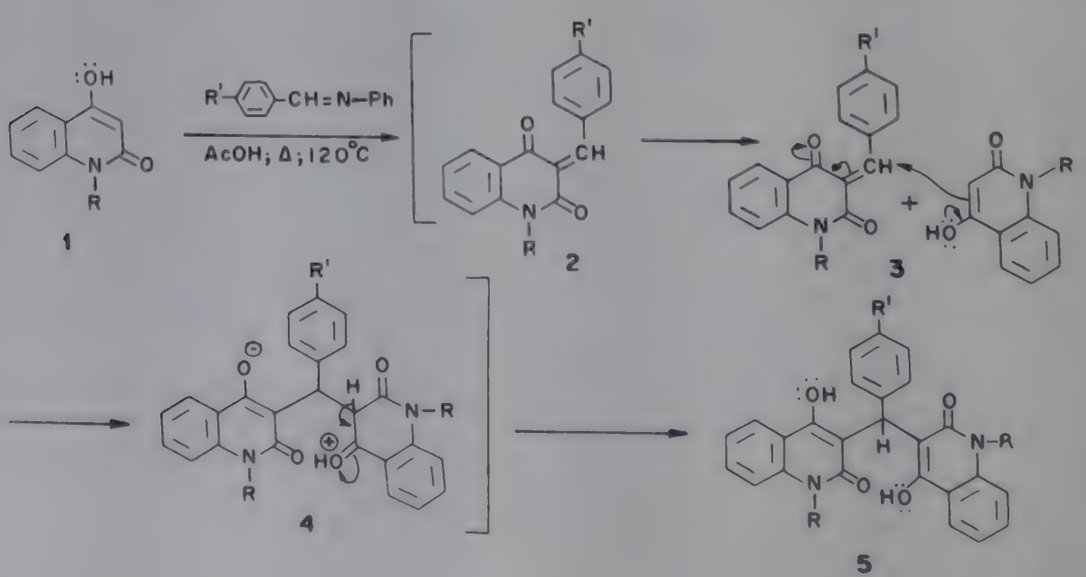
The compounds (**5a-e**) were obtained in one-step by the condensation of 4-hydroxy-1-methyl-2-quinolone[3] (**1**) with benzylidene anilines. Experimental conditions have been optimised to obtain maximum yield. The structures of the products were established by UV, IR and PMR data. For example compound (**5a**) exhibited in its UV spectrum in methanol peaks at 225 nm (log ε 4.9), 296 (4.2) 310 (4.2) and 330 (4.2) indicating the presence of extended conjugation. Its IR spectrum displayed peaks at 3020 (OH) and a high intensity split carbonyl absorption at 1610 and 1625 cm^{-1}. PMR spectrum **5a** displayed signals at δ 3.7 (*s*, 3H, N $-CH_3$), 3.8 (*s*, 3H, N $-CH_3$), 6.4 (*s*, 1H, on tertiary bridged carbon), 7.1-7.6 (*m*, 11H, aromatic), 8.2 (*m*, 2H aromatic on C-5 and C-5′), 12.4 (*s*, 1H, $-OH$) and 12.8 (*s*, 1H, $-OH$). The hydroxy protons were exchangeable with D_2O. In addition to the molecular ion, the mass spectrum showed other ions at *m/z* 263 (75%), 262 (100%), 175 (48%) and 77 (15%).

Under similar conditions, 4-hydroxy-1-phenyl-2-quinolone[8] (**1**) afforded products (**5f-j**). The above cited quinolones and schiff bases were warmed on a steam-bath using acetic acid as solvent. **5a** could also be obtained by refluxing **1** with benzaldehyde in *n*-butanol. All the reactions were axiomatic, since the formation of product (**5a**) proceeded through same intermediate (**2**) which could not be isolated.

The formation of **5** can be rationalised as follows: 4-Hydroxy-1-methyl/phenyl-2-quinolone (**1**) is acidic and reacts with one mol of protonated schiff base to form **2** as an intermediate by elimination of aniline as a better leaving group[9] The intermediate (**2**) being unstable and reactive adds on another molecule of 1 to form **5** through intermediates (**3**) and (**4**) (Scheme 1). 4-Hydroxycoumarin undergoes similar condensation to form dicoumarol[10]. However, the overall reactivity of **1** is found to be less than that of 4-hydroxycoumarins, since the condensation in this study requires higher temperatures and longer reaction time. The compounds (**5a-j**) thus synthesised are listed in Table 1.

Synthesis of 3,3′-*benzylidenebis*[4-*hydroxy*-1-*methyl*/-*phenyl*-2-*quinolones*] (**5**): (*i*) *Reaction in n-butanol*

A mixture containing 4-hydroxy-1-methyl-2-



SCHEME 1

Table 1—Characterisation Data of 3,3′-Benzylidenebis[4-hydroxy-1-methyl/phenyl-2-quinolones]

Compd No.	R	R′	m.p. °C (Recrystn. solvent)	Yield (%)	Mol. formula (M^+)	Found (%) (Calc.) C	H	N
5a	$-CH_3$	$-H$	295 (E.A)[a]	67	$C_{27}H_{22}N_2O_4$ (438)	74.25 (73.94)	5.36 (5.06)	6.08 (6.39)
5b	$-CH_3$	$-CH_3$	223 (P.E+C)[a]	62.5	$C_{28}H_{24}N_2O_4$	74.00 (74.30)	5.03 (5.34)	5.88 (6.19)
5c	$-CH_3$	$-OCH_3$	244 (E.A)[a]	69	$C_{28}H_{24}N_2O_5$	72.07 (71.76)	4.85 (5.16)	5.67 (5.98)
5d	$-CH_3$	$-Cl$	227 (P.E+C)[a]	26	$C_{27}H_{21}ClN_2O_4$ (472)	68.85 (68.54)	4.78 (4.47)	5.61 (5.92)
5e	$-CH_3$	$-NO_2$	287 (E.A)[a]	65	$C_{27}H_{21}N_3O_6$	67.36 (67.05)	4.07 (4.39)	8.98 (8.69)
5f	$-Ph$	$-H$	315 (E.A)[a]	43	$C_{37}H_{26}N_2O_4$ (562)	79.28 (78.97)	4.97 (4.66)	4.68 (4.98)
5g	$-Ph$	$-CH_3$	338 (P.E+C)[a]	53	$C_{38}H_{28}N_2O_4$ (576)	78.81 (79.13)	5.20 (4.89)	5.16 (4.85)
5h	$-Ph$	$-OCH_3$	340 (E.A)[a]	48	$C_{38}H_{28}N_2O_5$	76.67 (76.99)	4.45 (4.76)	5.03 (4.72)
5i	$-Ph$	$-Cl$	325 (P.E+C)[a]	37	$C_{37}H_{25}ClN_2O_4$	74.72 (74.40)	4.53 (4.22)	4.99 (4.69)
5j	$-Ph$	$-NO_2$	307 (E.A)[a]	53	$C_{37}H_{25}N_3O_6$	72.81 (73.12)	4.47 (4.22)	7.23 (6.91)

a) E.A = Ethyl acetate; P.E = Petroleum ether and C = Chloroform.

quinolone (0.87 g, 0.005 mol) and freshly distilled benzaldehyde (0.5 ml, 0.0025 mol) in *n*-butanol (25 ml) was refluxed for 3 hr. The product (**5**) that separated on cooling was filtered and recrystallised from appropriate solvent (see Table 1) using animal charcoal.

(ii) Reaction in acetic acid

(a) A mixture of (**1**, 0.87 g, 0.005 mol) and freshly distilled benzaldehyde (0.5 ml, 0.0025 mol) in acetic acid (35 ml) was refluxed for 3 hr. The crude product that separated on cooling was filtered and recrystallised. Compounds obtained by this method were identical to those obtained above.

(b) A mixture of **1** (0.005 mol) and appropriate schiff base (0.5 gr, 0.0025 mol) in acetic acid (20 ml) was refluxed in an oil-bath at 120° for 6 hr. The contents were cooled, filtered and the crude product (**5**) recrystallised.

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Stereochemical Assignment of 2,3-Dicarboxy-4-isopropyl-1-methylbicyclo[2.2.2]-oct-5-ene Anhydride through Conformational Analysis about N – N Bond by PMR Spectroscopy

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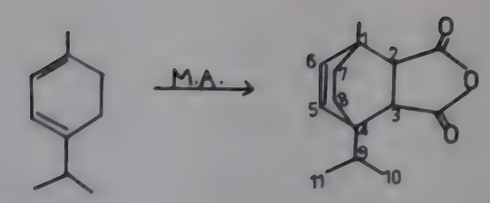
α-Terpinene and maleic anhydride give only one isomeric adduct which is shown to be *endo* through the PMR spectral studies of its N-acylhydrazide derivatives. The spectrum of N′-acetyl-N′-benzoylhydrazine derivative exhibits multiplicity in the olefinic region providing an unambiguous proof for the *endo*-geometry of the molecule.

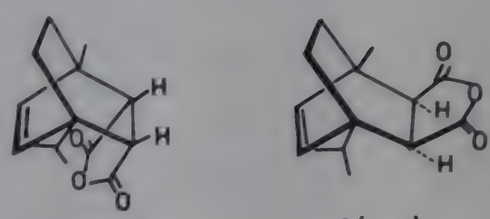
α-Terpinene (**1**) undergoes Diels-Alder reaction with maleic anhydride to yield 2,3-dicarboxy-4-isopropyl-1-methylbicyclo[2.2.2]oct-5-ene anhydride (I)[1], the structure of which has been established on the basis of its retro Diels-Alder reaction[2], thermolytic processes[3-5] and mass spectral studies[6,7]. Only one isomeric product (I) has been obtained and its stereochemistry as *endo* (**2**) or *exo* (**3**) remains unsettled.

Hindered rotation and non-planar conformation about the N – N bond in N′,N′-diacylhydrazine moiety of Diels-Alder adducts provide valuable informations about the stereochemistry of the adducts and are used successfully for their configurational (*endo/exo*) assignments[8,9]. This technique is found to be helpful in direct determination of the configuration[10,11] of either the *endo*- or *exo*-adduct without comparing the pattern of the other isomeric product. In this note, the stereochemistry of the Diels-Alder adduct (I) has been demonstrated with the help of its acylhydrazide and diacylhydrazine derivatives (II-VII; Table 1) through the conformations afforded by N′-substituents.

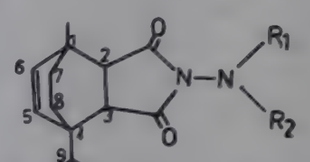
The PMR spectrum of I showed a double doublet for 10- and 11-methyl protons (0.98, 1.08, 6H, $J = 5$ Hz), a quartet for 7- and 8-methylene protons (1.36, 4H), a singlet for C_1-methyl protons (1.46, 3H), a multiplet for 9-H (2.60, 1H), an *AB* quartet for 2- and 3-H ($\delta A = 3.20$, $\delta B = 2.80$, 2H, $J_{AB} = 9$ Hz) and a multiplet for 5- and 6-protons (5.96, 2H). The spectral pattern shows the diastereotopic nature of 2,3-methine and the isopropyl methyl protons[12] due to the intrinsic asymmetry of the cage moiety. In this system the shielding parameter of the α-hydrogens to the carbonyl could not be helpful in the configurational assignment (*endo/exo*) of the adduct[13]. The configuration of a number of Diels-Alder adducts has been demonstrated through the spectral behaviour of their N′,N′-diacetyl derivative (type IV)[8-12]. The spectrum of IV exhibited two sharp



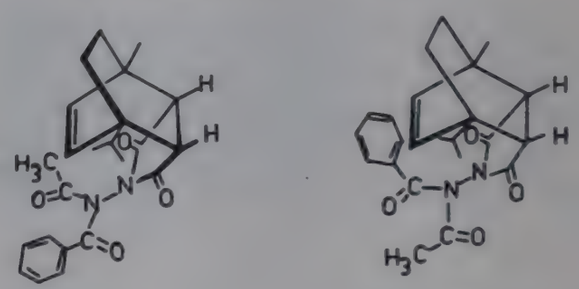
1 I



2 (endo) 3(exo)



II $R_1=R_2=H$
III $R_1=H, R_2=COCH_3$
IV $R_1=R_2=COCH_3$
V $R_1=H, R_2=COC_6H_5$
VI $R_1=COCH_3, R_2=COC_6H_5$
VII $R_1=R_2=COC_6H_5$



4 5

Table 1 – Characterization Data of Compounds II-VII

Compd	m.p. °C	Mol. formulae	Found (%) (Calc.)	
			C	H
II	148-49	$C_{14}H_{20}N_2O_2$	67.5 (67.7	7.8 8.1)
III	205-6	$C_{16}H_{22}N_2O_3$	66.0 (66.2	7.5 7.6)
IV	215-16	$C_{18}H_{24}N_2O_4$	65.3 (65.1	7.1 7.2)
V	115-17	$C_{21}H_{24}N_2O_3$	71.4 (71.6	6.5 6.8)
VI	147-48	$C_{23}H_{26}N_2O_4$	70.1 (70.1	6.3 6.6)
VII	105-6	$C_{28}H_{28}N_2O_4$	73.5 (73.7	6.0 6.1)

Table 2 – PMR Spectral Data of Compounds II-VII
[Chemical shifts in δ, ppm]

Compd	10- and 11-CH_3	7- and 8-methylene protons	C_1-CH_3	9-H	2- and 3-H	5- and 6-H	R_1 and R_2
II	0.98,1.10 (*dd*,6H,J = 7 Hz)	1.33 (*q*,4H)	1.52 (*s*,3H)	2.70 (*m*,1H)	AB_q (δA = 3.0,δB = 2.70, 2H,J = 8 Hz)	6.06 (*m*,2H)	7.30 (*bs*,2H)
III	0.98,1.10 (*dd*,6H,J = 7 Hz)	1.35 (*q*,4H)	1.50 (*s*,3H)	2.70 (*m*,1H)	AB_q (δA = 3.0,δB = 2.70, 2H,J = 8 Hz)	6.06 (*m*,2H)	2.54(*s*,3H) 7.30(*bs*,1H)
IV	1.01,1.11 (*dd*,6H,J = 6.5 Hz)	1.40 (*q*,4H)	1.52 (*s*,3H)	2.40 (*m*,1H)	AB_q (δA = 3.16,δB = 2.82 2H,J = 9 Hz)	6.03 (*m*,2H)	2.06,2.54 (*ds*,6H,1:1)
V	0.92,1.02 (*dd*,6H,J = 7 Hz)	1.35 (*q*,4H)	1.42 (*s*,3H)	2.50 (*m*,1H)	AB_q (δA = 3.05,δB = 2.65, (2H,J = 8 Hz)	5.92 (*m*,2H)	7.25-7.80 (*m*,6H)
VI	1.0 (*m*,6H)	1.35 (*q*,4H)	1.50 (*s*,3H)	2.40 (*m*,1H)	2.70 (*m*,2H)	5.08,6.03 (*dm*,2H,2:3)	2.40,2.57 (*ds*,6H,3:2), 7.30-7.70 (*m*,5H)
VII	0.92,1.10 (*dd*,6H,J = 7 Hz)	1.35 (*q*,4H)	1.50 (*s*,3H)	2.45 (*m*,1H)	AB_q (δA = 3.05,δB = 2.82, 2H,J = 8 Hz)	5.94 (*m*,2H)	7.20-7.80 (*m*,10H)

singlets for the two acetyl groups (2.08, 3H and 2.46, 3H) alongwith other proton resonances (Table 2). The multiplicity in the acetyl signals indicated restricted rotation and non-planar conformation about the N – N bond. In the case of *endo*-configuration (**2**), one of the acetyls would be under the anisotropic interaction of the olefinic bond, while in the *exo*-configuration (**3**), it would be in the vicinity of the ethylenic bridge. This is a limiting case where the shielding parameters in both the cases are of equal magnitude[10] ($\Delta\delta \simeq 0.2$ ppm) and the observed spectral pattern could not provide any valuable information about the geometry of the molecule.

The PMR spectrum of VI with dissimilar substituents, i.e. N′-acetyl-N′-benzoyl derivative showed a multiplet for 10- and methyl protons (1.0, 6H), a multiplet for 2- and 3-H (2.70, 2H), a double multiplet for 5- and 6-H (5.08, 6.03, 2H, 2:3) and double singlets for acetyl protons (2.40, 2.57, 3H, 3:2) alongwith other proton resonances (Table 2). Multiplicities in the acetyl and olefinic resonances showed clearly the existence of two conformers (**4** and **5**) due to slow rotation about the N – N bond at the PMR time scale. The splitting in the olefinic resonances suggests the N′-acyl substituents to be *syn* to the olefinic bond and demonstrates clearly the *endo*-geometry (**2**) for the Diels-Alder adduct. The population of the conformer **4**, where the acetyl group is *endo* to the cage olefinic bond is greater than the other conformer (**5**). The multiplicities in 4-isopropyl methyl further support the *endo*-configuration for the adduct. In the case of other isomeric adduct *exo* (**3**), the 7- and 8-methylene protons would have been under the anisotropic interaction of benzoyl group. The spectral behaviour of other N′-acyl derivatives (III, V and VII) did not exhibit a clear interaction of the N′-substituents with the olefinic protons and were not effective probes for the configurational assignment.

PMR spectra were recorded on a Jeol FX 90 Q spectrometer at 25° in $CDCl_3$ using TMS as internal standard (chemical shift in δ, ppm), and IR spectra in nujol mull on a Perkin-Elmer 720 spectrophotometer (ν_{max} in cm^{-1}).

2,3-*Dicarboxy*-4-*isopropyl*-1-*methylbicyclo*-[2.2.2]-*oct*-5-*ene anhydride* (*I*)

It was prepared following the method of Ipatieff and Pines[6] and crystallized from aq. ethanol, m.p. 65° (lit.[6] m.p. 64-65°); IR: 1870m, 1840s, 1780s.

Hydrazide (*II*) *of the adduct*

It was obtained by stirring an ethanolic solution of the adduct I (2.2 g in 20 ml) with hydrazine hydrate (0.5 ml) for 2 hr at room temperature. The solid obtained was filtered and recrystallized from aq. ethanol.

N′-Monoacetylhydrazide (*III*)

It was obtained by refluxing the adduct hydrazide II with an excess of acetic acid and a few drops of pyridine for 3 hr. The solvent was removed under reduced pressure, and the resultant solid washed with water and recrystallized from aq. ethanol.

N′,N′-Diacetylhydrazine derivative (*IV*)

It was obtained by refluxing II with an excess of acetic anhydride in the presence of a few drops of

pyridine for 3 hr. The solvent was removed under reduced pressure and the solid obtained washed with water and recrystallized from ethanol.

N'-Acetyl-N'-benzoylhydrazine derivative (*VI*)

It was obtained in two steps. In the first step, N'-monobenzoylhydrazide (V) was prepared by refluxing II (1.0 g) with benzoyl chloride (0.6 ml) in dry benzene for about 4 hr. The solvent was removed under reduced pressure and the solid obtained washed with water and recrystallized from ethanol. In the second step, V was refluxed with acetic anhydride and a few drops of pyridine for 3 hr. The solvent was removed under reduced pressure and the solid obtained washed with water and recrystallized from ethanol.

N',N'-Dibenzoylhydrazine derivative (*VII*)

It was obtained by refluxing II (1.0 g) with an excess of benzoyl chloride (2.0 g) and a few drops of pyridine in dry benzene for 3 hr. The solvent was removed under reduced pressure and the residue washed with a dil. solution of sodium carbonate. The resultant solid was filtered, washed with water and recrystallized from ethanol.

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Synthesis & Biological Activities of 3-(2′-Aryl-4′-oxothiazolidin-3′-yl)-2-phenylquinazolin-4(3*H*)-ones

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A number of 3-(2′-aryl-4′-oxothiazolidin-3′-yl)-2-phenylquinazolin-4(3*H*)-ones (III) have been synthesised and screened for their possible antibacterial activity and CNS activity on albino mice. Some chemical leads towards structure-activity relationship have been established.

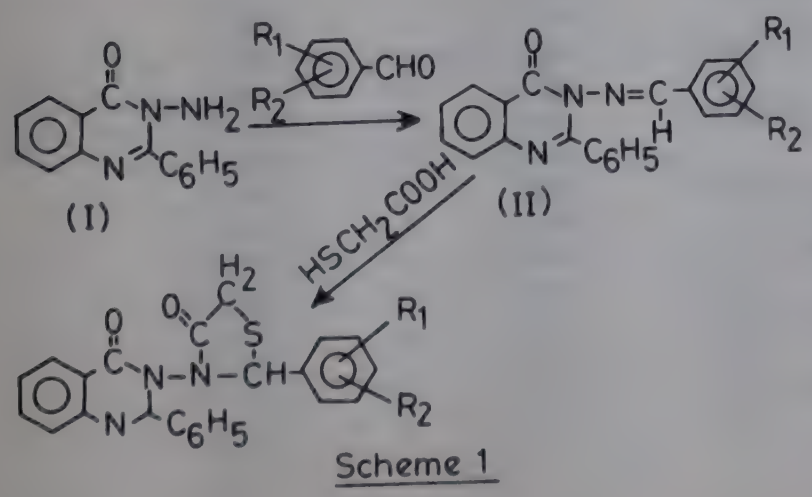
Thiazolidinones have been found to be CNS active[1] and antibacterial agents[2]. Numerous quinazolinone derivatives have also been shown to be CNS active agents[3] through their well known monoamine oxidase inhibitory effects on CNS, and a few of them exhibited antibacterial properties[4]. These reports prompted the authors to synthesise some substituted thiazolidinonyl quinazolinones with a presumption that the union of these two heterocyclic moieties would produce new compounds which could display better antibacterial and CNS active properties.

The synthesis of the title compounds (III) was accomplished as shown in Scheme 1 by the condensation of 3-arylideneamino-2-phenylquinazolin-4(3*H*)-ones (II) with mercaptoacetic acid. The compounds II and III (Table 1) were characterised by elemental analyses, IR and PMR spectroscopy.

Biological activities

(*a*) *Antibacterial activity*

The antibacterial screening of 3-arylideneamino-2-phenylquinazolin-4(3*H*)-ones (II) and 3-(2′-aryl-4′-thiazolidin-3′-yl)-2-phenylquinazolin-4(3*H*)-ones (III) against *Bacillus cereus*, *Staphylococcus aureus*, *Micrococcus flavus*, *Sarcina lutae* and *Bacillus subtilis* was carried out by the disc agar diffusion method of Varma and Nobles[5]. Based on the data given in Table 2, the following chemical leads became apparent.



Scheme 1

(i) The formation of thiazolidinone ring in compounds III from the respective aldimines (II) increases the antibacterial activity.

(ii) Substitution of electron attracting groups as well as methoxy group on phenyl ring at position-2 of thiazolidinone ring generally increases the antibacterial activities.

(iii) The presence of an electron donor substituent such as hydroxy or fluoro group at *ortho*-position in the phenyl ring at position-2 of thiazolidinone ring renders the compounds to have better activity than the *m*- and *p*-analogs. Moreover, compounds having 3,4-dihydroxy or dimethoxy substituents on the phenyl ring exhibit good antibacterial activities.

(iv) The compounds II and III are inactive against *B. subtilis*.

(*b*) *CNS activity*

The ALD_{50} values of 3-arylideneamino-2-phenylquinazolin-4(3*H*)-ones (IIc and IIe-h) and 3-(2-aryl-4-oxothiazolidin-3-yl)-2-phenyl-quinazolin-4(3*H*)-ones (IIIc, e, f-h, m) were determined in albino mice of either sex, weighing between 20 and 25 g. At 1/5th of ALD_{50}, the behavioural changes in CNS activities were also noted and are given in Table 3. All the compounds induced stimulatory effects except compounds IIg, IIIe and IIIn. Compounds, IIc, IIe, IIf, IIIc and IIIf caused an increased rate of breathing, while IIh, IIIe, IIIg, IIIh and IIIm affected the belly muscles as they induced writhing (twisting of belly) in test animals. Compounds IIg, IIh, IIIe, IIIg and IIIm also induced hypothermia, the most potent being IIIm which decreased the body temperature by 1.8°C; and hence they may be screened further as antipyretics. All the compounds were nontoxic except IIc, IIe, IIf and IIIc.

Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in CCl_4 on a Varian EM-360 instrument using TMS an an internal reference (chemical shifts in δ, ppm).

3-(2′-Fluorobenzylideneamino)-2-phenylquinazolin-4(3H)-ones (IIj)

3-Amino-2-phenylquinazolin-4(3*H*)-one[6] (I; 0.01 mol, 2.37 g) and 2-fluorobenzaldehyde (0.01 mol,

Table 1—Characterisation Data of 3-(Arylideneamino)-2-phenylquinazolin-4(3*H*)-ones (II) and 3-(2′-Aryl-4′-oxothiazolidin-3′-yl)-2-phenylquinazolin-4(3*H*)-ones

Compd	R^1	R^2	m.p.* (°C)	Mol. formula	Found (%) (Calc.)		
					C	H	N
IIa	H	4-CH_3	195-200	$C_{22}H_{17}N_3O$	77.6	5.2	12.1
					(77.9	5.0	12.0)
IIb	H	4-$N(CH_3)_2$	246	$C_{23}H_{20}N_4O$	75.2	5.6	15.4
					(75.0	5.4	15.2)
IIc	H	2-Cl	220	$C_{21}H_{14}N_3OCl$	70.2	3.6	11.5
					(70.0	3.9	11.7)
IId	H	2-OH	220	$C_{21}H_{15}N_3O_2$	73.8	4.5	12.5
					(73.9	4.4	12.3)
IIe	H	3-OH	218	$C_{21}H_{15}N_3O_2$	73.8	4.5	12.5
					(73.9	4.4	12.3)
IIf	H	4-OH	223	$C_{21}H_{15}N_3O_2$	73.7	4.3	12.5
					(73.9	4.4	12.3)
IIg	H	4-OCH_3	150	$C_{22}H_{17}N_3O_2$	74.5	4.9	12.0
					(74.4	4.8	11.8)
IIh	4-OH	3-OCH_3	162-5	$C_{22}H_{17}N_3O_3$	71.3	4.4	11.6
					(71.2	4.6	11.3)
IIi	3-OCH_3	4-OCH_3	202	$C_{23}H_{19}N_3O_3$	71.5	4.8	10.7
					(71.7	4.9	10.9)
IIj	H	2-F	170	$C_{21}H_{14}N_3OF$	73.2	4.2	12.5
					(73.5	4.1	12.2)
IIk	H	3-F	162-5	$C_{21}H_{14}N_3OF$	73.6	4.3	12.4
					(73.5	4.1	12.2)
IIl	H	4-F	190-5	$C_{21}H_{14}N_3OF$	73.6	4.2	12.4
					(73.5	4.1	12.2)
IIm	H	3-NO_2	288	$C_{21}H_{14}N_4O_3$	68.3	3.5	15.3
					(68.0	3.8	15.1)
IIn	H	4-NO_2	198	$C_{21}H_{14}N_4O_3$	68.2	3.6	15.4
					(68.1	3.8	15.1)
IIIa	H	4-CH_3	156	$C_{24}H_{19}N_3O_2S$	69.9	4.5	10.3
					(69.7	4.6	10.2)
IIIb	H	4-$N(CH_3)_2$	210	$C_{25}H_{22}N_4O_2S$	67.7	4.8	12.5
					(67.9	5.0	12.7)
IIIc	H	4-Cl	226	$C_{23}H_{16}N_3O_2SCl$	63.7	3.8	9.8
					(63.6	3.7	9.7)
IIId	H	2-OH	130	$C_{23}H_{17}N_3O_3S$	66.4	4.2	10.3
					(66.5	4.1	10.1)
IIIe	H	3-OH	214	$C_{23}H_{17}N_3O_3S$	66.4	4.3	10.3
					(66.5	4.1	10.1)
IIIf	H	4-OH	130	$C_{23}H_{17}N_3O_3S$	66.3	4.2	10.3
					(66.5	4.1	10.1)
IIIg	H	4-OCH_3	95	$C_{24}H_{19}N_3O_3S$	67.3	4.3	9.6)
					(67.1	4.4	9.8)
IIIh	4-OH	3-OCH_3	150-2	$C_{24}H_{19}N_3O_4S$	64.6	4.5	9.2
					(64.7	4.7	9.4)
IIIi	3-OCH_3	4-OCH_3	156-8	$C_{25}H_{21}N_3O_4S$	65.5	4.5	9.3
					(65.4	4.6	9.2)
IIIj	H	2-F	175	$C_{23}H_{16}N_3O_2SF$	66.3	3.7	10.2
					(66.2	3.8	10.1)
IIIk	H	3-F	205	$C_{23}H_{16}N_3O_2SF$	66.4	3.7	10.2
					(66.2	3.8	10.1)
IIIl	H	4-F	178	$C_{23}H_{16}N_3O_2SF$	66.3	4.0	10.2
					(66.2	3.8	10.1)
IIIm	H	3-NO_2	160	$C_{23}H_{16}N_4O_4S$	62.3	3.7	12.8
					(62.2	3.6	12.6)
IIIn	H	4-NO_2	215	$C_{23}H_{16}N_4O_4S$	62.3	3.5	12.5
					(62.2	3.6	12.6)

Table 2—Antibacterial Activities of 3-Arylideneamino-2-phenyl-quinazolin-4(3*H*)-ones (II) and 3-(2′-Aryl-4′-oxo-thiazolidin-3′-yl)-2-phenylquinazolin-4(3*H*)-ones (III)

Compd	R^1	R^2	Inhibition zone (in cm) against bacteria*				
			A	B	C	D	E
IIa	*p*-Cl	H	0.8	0.8	—	—	—
IId	*o*-OH	H	1.8	0.6	0.8	0.8	—
IIe	*m*-OH	H	0.8	—	—	—	—
IIf	*p*-OH	H	0.9	—	—	—	—
IIg	*m*-OCH_3	*p*-OH	1.2	0.9	0.6	0.7	—
IIi	*m*-OCH_3	*p*-OCH_3	1.0	0.7	0.6	0.7	—
IIj	*o*-F	H	1.0	0.8	0.8	0.8	0.7
IIk	*m*-F	H	—	—	—	—	—
IIm	*m*-NO_2	H	—	0.7	0.6	0.8	—
IIIa	*p*-CH_3	H	—	—	—	0.8	0.6
IIIc	*p*-Cl	H	1.0	0.8	—	0.6	—
IIId	*o*-OH	H	1.2	0.7	—	0.6	0.7
IIIe	*m*-OH	H	—	—	0.8	—	—
IIIf	*p*-OH	H	—	0.8	—	0.8	—
IIIg	*p*-OCH_3	H	0.6	0.8	—	0.8	—
IIIh	*m*-OCH_3	*p*-OH	1.6	1.0	0.7	0.8	—
IIIi	*m*-OCH_3	*p*-OCH_3	1.6	—	0.7	0.7	—
IIIj	*o*-F	H	1.1	—	1.3	0.6	0.7
IIIk	*m*-F	H	—	—	—	—	—
IIIl	*p*-F	H	—	—	0.8	—	0.6
IIIm	*m*-NO_2	H	2.1	—	0.8	—	—
IIIn	*p*-NO_2	H	—	—	0.8	0.7	—
Standard drug (Tetracycline)			3.6	2.4	2.5	2.4	2.0

*A = *B. cereus*; B = *S. aureus*; C = *M. flavus*; D = *S. lutae*; E = *B. subtilis*; (−) = no activity.

Table 3—ALD_{50} and Behavioural Changes in Gross CNS Activities of 3-Arylideneamino-2-phenylquinazolin-4(3*H*)-ones (II) and 3-(2′-Aryl-4′-oxothiazolidin-3′-yl)-2-phenylquinazolin-4(3*H*)-ones (III)

Compd	ALD_{50} (mg/kg i.p.)	Gross effects* at 0.2 of ALD_{50}				
		SMA†	React‡	Writning	Body temp. (°C)	Other effects
IIc	383	↑	↑	—	—	Resp↑
IIe	147	↑	↑	—	—	Resp↑
IIf	147	↑	↑	—	—	Resp↑
IIg	>1000	↓	↓	—	↓ 0.2	—
IIh	681	↑	↑	(+)	↓ 0.2	—
IIIc	147	↑	↑	(−)	—	Resp↑
IIIe	>1000	(30′-3 hr)	(30′-3 hr)	(+)	↓ 0.3	—
IIIf	681	↓	↓	—	—	Resp↑
		↑	↑			Tremor (+)
IIIg	>1000	↑	↑	(+)	↓ 0.2	—
IIIh	>1000	↑	↑	(+)	↓ 0.4	—
IIIm	>1000	↓	↓	(+)	↓ 1.8	—

* ↓ = decreased; ↑ = (increased; (+) = present; (−) = not affected
†SMA = Spontaneous motor activity.
‡React = Reactivity to sound and touch.
30′-3 hr = Effect of compound from 30 minutes to 3 hours

1.24 g) were dissolved in abs. methanol (10 ml), and acetic acid (2 drops) was added to this solution. The reaction mixture was refluxed for 4 hr. The solid that separated on cooling was filtered and recrystallised from methanol to give IIj, m.p. 170°; IR: 3050 (aromatic C−H), 1680 (C=O), 1620 (C=N).

Similarly, other members of the type II were prepared and their characterization data are given in Table 1. The yields were in the range of 75-90%.

3-[2′-(*o-Fluorophenyl*-4′-*oxothiazolidin*-3′-*yl*]-2-*phenylquinazolin*-4(3*H*)-*one* (*IIIj*)

To a solution of IIj (0.005 mol, 2.21 g) in anhyd. benzene (10 ml) was added mercaptoacetic acid (0.006

mol, 0.55 ml) and the reaction mixture refluxed for 9 hr. The solid that separated on cooling was filtered, excess of mercaptoacetic acid removed by washing it repeatedly with saturated aq. sodium bicarbonate solution and recrystallised from ethyl acetate to give IIIj, yield 60%, m.p. 175°; IR: 3050 (aromatic C−H) 2950 (C−H stretch of CH at position-2 of thiazolidinone ring), 2900 (C−H stretch of CH_2 at position-5 of thiazolidinone ring), 1680 (broad with a shoulder, C=O), 1610 (C=N); PMR(CCl_4): 2.04 (*s*, 2H, 5-CH_2 of thiazolidinone moiety), 3.50 (*s*, 1H, 3-H of thiazolidinone moiety) and 6.9-8.95 (complex *m*, 13H, Ar−*H*).

The characterization data of other members of the series III, obtained in 62-74% yields, are given in Table 1.

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Synthesis & Biological Activities of 3-Aryl-5-(aryliminoethylideneamino)-4-oxothiazolidine-2-thiones

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The title compounds (VII, VIII) have been prepared by the schiff base formation between 2-[3-aryl-4-oxo-2-thioxothiazolidin-5-ylimino]acetaldehyde and different primary amines, and screened for their antibacterial activity against *B. cereus*, *S. aureus*, *M. flavus*, *S. lutae* and *B. subtilis* and antiviral activity against Tobacco Mosaic Virus. Some of the compounds show moderate antibacterial and antiviral activities.

3-Substituted rhodanines and iminothiazolidinones have been found to be antibacterial[1,2] and antiviral[3,4] agents. The schiff bases act as antibacterial agents[5] due to their chelating property[6]. Moreover, the complex formation of ethylenediamine and its derivatives is well known[7], and presumably due to this many such compounds[8] and double schiff bases[9] exhibit antibacterial activity. Hence, it was considered worthwhile to synthesise the title compounds and study their antibacterial and antiviral activities.

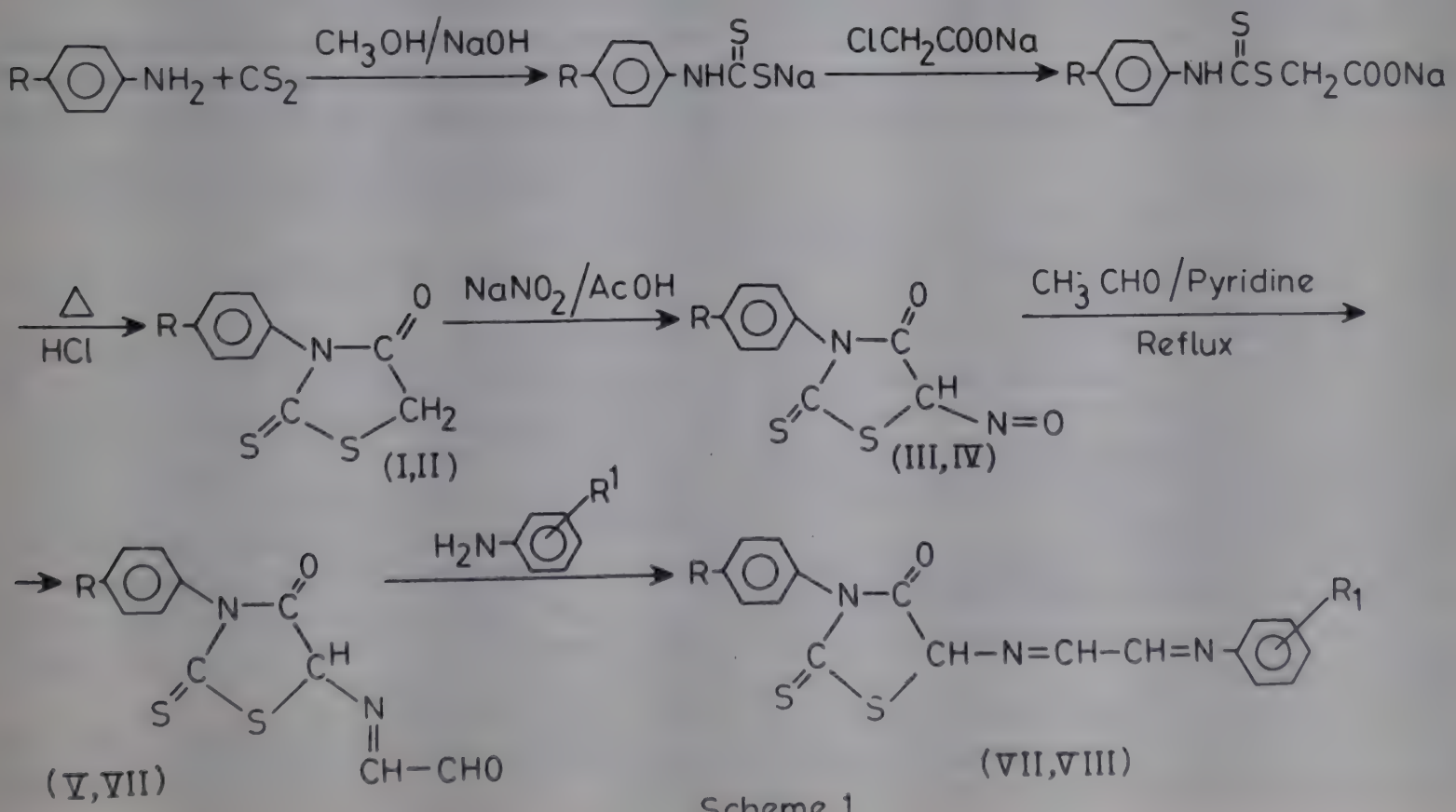
The reaction sequence leading to the title compounds is given in Scheme 1. The intermediate 3-aryl-5-nitrosorhodanines (III, IV), prepared by the nitrosation of 3-arylrhodanines (I, II), on treatment with acetaldehyde in the presence of pyridine gave 2-(3-aryl-4-oxo-2-thioxothiazolidin-5-ylimino)-acetaldehydes (V, VI) through a carbanion mechanism parallel to that of Perkin or Knoevenagel reaction. In the final step, the iminoacetaldehyde (V, VI) underwent schiff base formation with arylamines to give the desired compounds (VII, VIII; Table 1).

Biological Activities

(*a*) *Antibacterial activity*

Fifteen compounds (VIIa-g, VIIIi, j and VIIIa-f) were screened for their *in vitro* antibacterial potentiality against *B. cereus*, *S. aureus*, *M. flavus*, *S. lutae* and *B. subtilis* following the disc agar diffusion technique of Varma and Nobles[12]. The inhibition zones (in cm) of these compounds against the above bacteria are given in Table 1. For comparison, the inhibition zones of the standard antibacterial drug tetracycline against the test bacteria are also given in Table 1.

All the test compounds were found to show moderate (but weaker than tetracycline) antibacterial activity except compound VIId. From the data given in Table 1, it is clear that the effect of substituents 'R^1' on the phenyl ring in the side chain at position-5 of rhodanine nucleus, gives some directive towards the



Scheme 1

Table 1—Characterisation Data and Antibacterial and Antiviral Activities of 3-Aryl-5-(arylimino thylideneamino)-4-oxothiazolidine-2-thiones (VII and VIII)

Compd*	R^1	m.p. (°C)	Yield (%)	Mol. formula	Inhibition zone (in cm) against the bacteria†					% inhibition of Tobacco Mosaic Virus
					A	B	C	D	E	
				$R=CH_3$						
VIIa	H	101	61	$C_{18}H_{15}N_3OS_2$	0.6	—	—	—	—	9
VIIb	2-CH_3	95	66	$C_{19}H_{17}N_3OS_2$	0.6	—	0.7	—	0.6	38
VIIc	3-CH_3	102	72	$C_{19}H_{17}N_3OS_2$	0.9	1.0	—	—	—	ns
VIId	4-CH_3	138	75	$C_{19}H_{17}N_3OS_2$	—	—	—	—	—	18
VIIe	2-OCH_3	88	78	$C_{19}H_{17}N_3O_2S_2$	0.6	0.6	—	0.6	0.7	54
VIIf	3-OCH_3	105	63	$C_{19}H_{17}N_3O_2S_2$	0.6	0.8	—	—	—	ns
VIIg	4-OCH_3	140	67	$C_{19}H_{17}N_3O_2S_2$	0.6	—	0.8	—	—	42
VIIh	3-Cl	108	70	$C_{18}H_{14}N_3OS_2Cl$	0.7	0.8	—	—	—	ns
VIIi	4-Cl	123	77	$C_{18}H_{14}N_3OS_2Cl$	0.7	0.6	0.7	0.9	0.6	41
				$R=OCH_3$						
VIIIa	H	115	74	$C_{18}H_{15}N_3O_2S_2$	ns					
VIIIb	2-CH_3	120	66	$C_{19}H_{17}N_3O_2S_2$	—	—	1.0	—	—	26
VIIIc	3-CH_3	98	63	$C_{19}H_{17}N_3O_2S_2$	0.6	—	—	—	—	ns
VIIId	4-CH_3	144	62	$C_{19}H_{17}N_3O_2S_2$	0.6	—	—	0.8	—	59
VIIIe	2-OCH_3	91	78	$C_{19}H_{17}N_3O_3S_2$	0.6	0.3	1.0	—	—	16
VIIIf	3-OCH_3	117	72	$C_{19}H_{17}N_3O_3S_2$	—	—	—	0.9	—	ns
VIIIg	4-OCH_3	128	76	$C_{19}H_{17}N_3O_3S_2$	—	—	0.6	0.5	—	39
VIIIh	3-Cl	103	75	$C_{18}H_{14}N_3O_2S_2Cl$	ns					
VIIIi	4-Cl	112	76	$C_{18}H_{14}N_3O_2S_2Cl$	ns					
Tetracycline (standard)					3.6	2.4	2.5	2.4	2.0	

*All the compounds analysed satisfactorily for C, H and N

†A = *B. cereus*; B = *S. aureus*; C = *M. flavus*; D = *S. lutae*; E = *B. subtilis*, (−) = no activity; ns = not screened.

chemical leads on these variations. Thus, compound VIIa, in which $R^1=H$, produces the lowest inhibition zone towards all the test bacteria. The substitution of CH_3, Cl or OCH_3 group as R^1 increases the antibacterial potentiality of resultant compounds.

(*b*) *Antiviral activity*

Ten compounds of the series 3-aryl-5-(arylimino-ethylideneamino)-4-oxothiazolidine-2-thiones (viz. VIIa,b, VIId,e VIIg, VIIj, VIIIa, VIIIc,d and VIIIf) were tested for their antiviral activity against *Tobacco Mosaic Virus* (TMV) on *N. glutinosa* leaves as host by the method of Verma and Awasthi[13]. The compounds were dissolved in methanol and the final concentration of test compounds was 2.5 mg/ml. The data of antiviral activity are given in Table 1.

All the test compounds were found to exhibit good antiviral activity except compounds VIIa, VIId, VIIIa and VIIId. The antiviral activity data led to the following generalizations:

(i) The antiviral activity was found to depend on the nature of the substituent 'R'. In compounds having $R=CH_3$, the antiviral potentiality was found to be more than in compounds having $R=OCH_3$ (except compounds VIId and VIIIc).

(ii) Amongst compounds VIIa-j, the compound VIIa having $R^1=H$ exhibited the least antiviral activity (9%), while the substitution of R^1 by other groups increased the activity. The antiviral activity was found to increase with the increasing electronegativity (χ) of substituents, i.e.

$H(\chi_H=2.0)<CH_3(\chi_C=2.5)<Cl(\chi_{Cl}=3.0)<OCH_3(\chi_O=3.5)$

(iii) When $R=CH_3$, the electronegative groups at R^1 in compounds VII brought about enhancement in the antiviral potentiality, while this trend was found to be reversed when $R=OCH_3$, i.e. in compounds VIII.

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer-157 spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in $CDCl_3$ on a Varian A60D instrument using TMS as internal standard (chemical shifts in δ, ppm).

The required 3-(*p*-tolyl)rhodanine(I)[10] and 3-(*p*-anisyl)rhodanine (II)[11] were prepared by literature methods.

3-*Aryl*-5-*nitrosorhodanines* (*III and IV*)

To an ice cold solution of I (0.1 mol) in acetic acid (40 ml), sodium nitrite (0.2 mol) was added in small portions (0.5 g each) with vigorous shaking, and the resultant solution kept at room temperature overnight. It was then poured into crushed ice (200 gms), and the separated solid filtered, washed well and recrystallised from benzene-pet. ether (60-80°) to give III, yield 80%, m.p. 154° (Found: C, 47.5; H, 3.52; N, 11.3. $C_{10}H_8N_2O_2S_2$ requires C, 47.6; H, 3.2 and N, 11.1%); IR: 3050, 2900, 2850, 1730, 1540, 1230.

Similarly, 2-(*p*-anisyl)-5-nitrosorhodanine (IV) was prepared by nitrosation of 3-(*p*-anisyl)rhodanine (IV).

2-[4-*Oxo*-2-*thioxo*-3-(*p*-*tolyl*)*thiazolidin*-5-*ylimino*]*acetaldehyde* (*V*)

To a solution of III (0.05 mol) in pyridine (40 ml) was added acetaldehyde (0.065 mol), the reaction mixtures stirred overnight and poured into a mixture of ice (200 g) and conc. HCl (100 ml). The solid separated was filtered, washed well with water, dried and recrystallised from ethyl acetate-pet. ether (60-80°) to give V, yield 60%, m.p. 135° (Found: C, 51.8; H, 3.4; N, 10.3. $C_{12}H_{10}N_2O_2S_2$ requires, C, 51.8; H, 3.6; N, 10.1%); IR: 3030, 2960, 2920, 1720, 1700, 1680, 1590 and 1235, etc.

Similarly, 2-[3-(*p*-anisyl)-4-oxo-2-thioxothiazolidin-5-ylimino]acetaldehyde (VI) was also prepared, yield 65%, m.p. 123° (Found: C, 48.7; H, 3.6; N, 9.6. $C_{12}H_{10}N_2O_3S_2$ requires C, 49.0; H, 3.4; N, 9.5%).

3-*Aryl*-5-(*aryliminoethylideneamino*)-4-*oxo*-*thiazolidine*-2-*thiones* (*VII and VIII*; *Table* 1)

To a solution of V (0.005 mol) in methanol (10 ml) was added *p*-toluidine (0.005 mol) and the reaction mixture refluxed on a water-bath for 4 hr. It was poured into ice, and the separated solid filtered, dried and triturated with pet. ether (60-80°). The residue was recrystallised from ethyl acetate to give VIId, yield 75%, m.p. 138° (Found: C, 62.3; H, 4.5; N, 11.6. $C_{19}H_{17}N_3OS_2$ requires C, 62.1; H, 4.6; N, 11.4%); IR: 3060, 2950, 1730, 1690, 1620, 1250; PMR: 1.3 (*s*, 3H, $C_6H_5CH_3$ at position-3 of thiazolidinone moiety), 2.3 (*s*, 3H, $C_6H_5-CH_3$ in the side chain at position-5 of thiazolidinone moiety), 3.70 (*s*, 2H, $-N-CH-CH=N-$), 3.85 (*s*, 1H, thiazolidinone 5-*H*) 6.9-7.25 (complex *m*, 8H, $2-N-C_6H_4-CH_3$).

Similarly, other members of the series VII and VIII were prepared by the reactions of appropriate arylamines with relevant V, VI.

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Synthesis & Biological Activities of 3-(N,N-Disubstituted aminomethyl)-5-[(6,8-disubstituted-4-oxoquinazolin-3-yl)imino]-4-oxo-1,3-thiazolidine-2-thiones

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Twenty-two title compounds (VIII and IX) have been synthesised by carrying out the Mannich reaction between 5-[(6,8-disubstituted-4-oxoquinazolin-3-yl)imino]-4-oxo-1,3-thiazolidine-2-thione and various secondary amines. Some of the compounds show moderate antibacterial and antiviral activities.

Quinazolinones have been found useful as antibacterial[1] and antiviral[2] agents. Rhodanine derivatives have also shown good antibacterial[3] and antiviral activities[4]. Moreover, it has been found that the formation of a Mannich base on rhodanine nucleus enhances the above activities[5]. Hence, it was considered of interest to synthesise compounds which are the Mannich bases of substituted rhodanines. The synthesis of such compounds is described in this note.

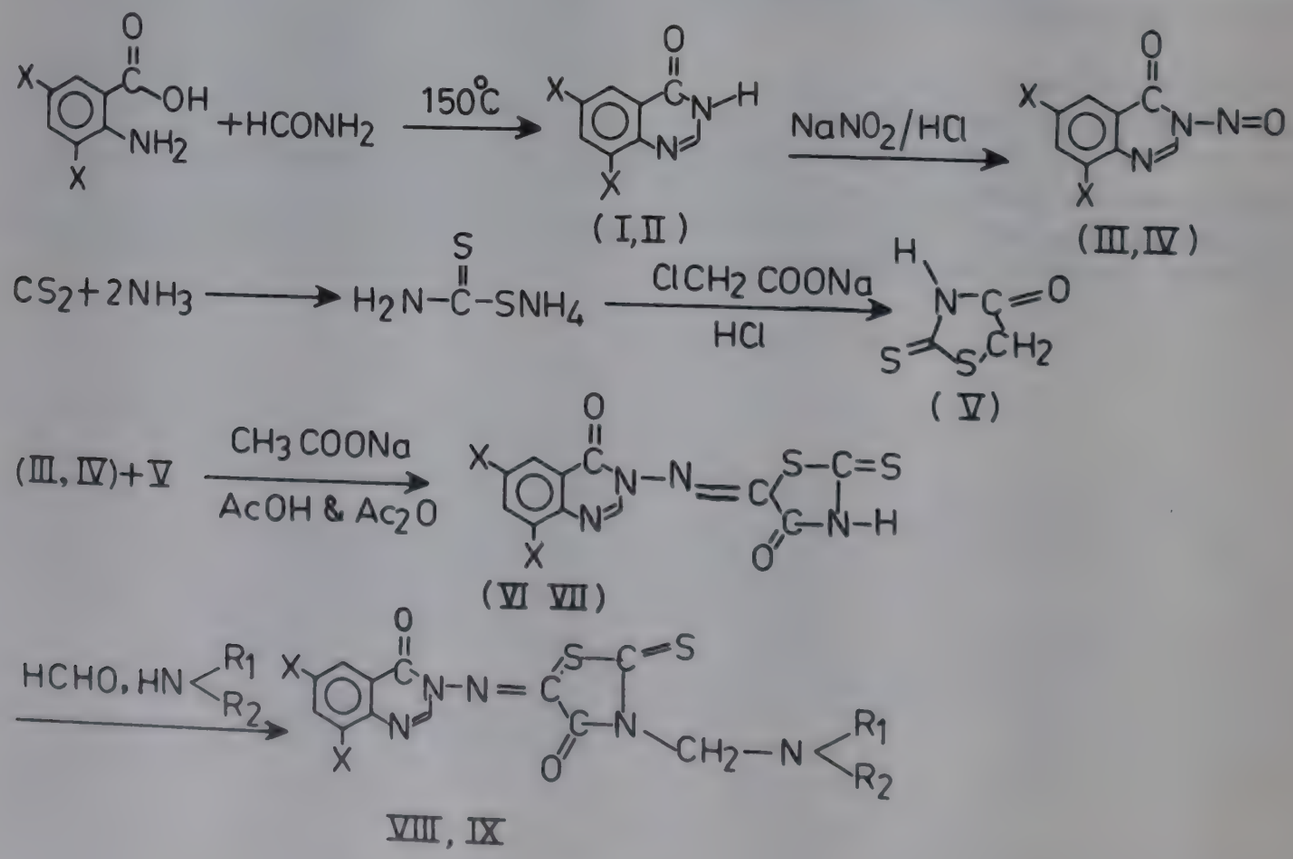
The intermediate compounds 5-(4-oxo-quinazolin-3-yl)imino-4-oxothiazolidine-2-thiones (VI and VII) were prepared by the Knoevenagel type condensation between 3-nitrosoquinazolinones (III, IV) and rhodanine (V). These compounds (VI, VII) on Mannich reaction with various secondary amines and formaldehyde afforded the title compounds (VIII and IX; Scheme 1) which were characterised by elemental analyses (Table 1) and spectral data (IR and PMR).

ological Activities

Antibacterial activity—Seventeen compounds viz. VIIIa, VIIIb, VIIId, VIIIg,h and VIIIj,k and IXa-j were screened for their antibacterial activity *in vitro* against *Bacillus cereus*, *Staphylococcus aureus*, *Micococcus flavus*, *Sarcina lutea* and *Bacillus subtilis* by the disc agar diffusion method of Varma and Nobles[6] employing tetracycline as a standard antibacterial drug. The results given in table 2 indicate that:

(i) 6,8-Dibromoquinazolone derivatives (IX) are weaker agents against the tested bacteria than the corresponding unsubstituted quinazolones (VIII).

(ii) Compounds having alkylamino substituents at



Scheme 1

Table 1—Characterization Data of 3-(N,N-Disubstituted aminomethyl)-5-[(6,8-disubstituted-4-oxoquinazolin-3-yl)imino]-4-oxo-1,3-thiazolidine-2-thiones (VIII and IX)

Compd	$N\langle^{R^1}_{R^2}$	m.p.* °C	Yield (%)	Mol. formula	Found (%) (Calc.)		
					C	H	N
			X = H				
VIIIa	Dimethylamino	268	80	$C_{14}H_{13}N_5O_2S_2$	48.2	3.6	20.3
					(48.4	3.7	20.2)
VIIIb	Diethylamino	277-9	83	$C_{16}H_{17}N_5O_2S_2$	51.0	4.3	18.8
					(51.2	4.5	18.7)
VIIIc	Dibenzylamino	284	76	$C_{26}H_{21}N_5O_2S_2$	62.3	4.4	14.3
					(62.5	4.2	14.0)
VIIId	Diethanolamino	300	75	$C_{16}H_{17}N_5O_4S_2$	47.3	4.3	17.4
					(47.2	4.2	17.2)
VIIIe	Piperidino	306	79	$C_{17}H_{19}N_5O_3S_2$	50.1	4.8	17.1
					(50.4	4.7	17.3)
VIIIf	Morpholino	294	82	$C_{16}H_{15}N_5O_3S_2$	49.5	4.0	17.8
					(49.4	3.9	18.0)
VIIIg	N-Methylpiperazino	280	78	$C_{17}H_{18}N_6O_2S_2$	50.6	4.6	20.6
					(50.7	4.5	20.9)
VIIIh	N-Phenylpiperazino	286	85	$C_{22}H_{20}N_6O_2S_2$	56.7	4.5	18.3
					(56.9	4.3	18.1)
VIIIi	N-*p*-Chlorophenyl-piperazino	288-90	83	$C_{22}H_{19}N_6O_2S_2Cl$	52.7	4.0	17.0
					(52.9	3.8	16.8)
VIIIj	N-Methylanilino	301-2	74	$C_{19}H_{15}N_5O_2S_2$	55.6	3.9	17.2
					(55.7	3.7	17.1)
VIIIk	N-Ethylanilino	279	72	$C_{20}H_{17}N_5O_2S_2$	56.6	4.3	16.4
					(56.7	4.0	16.5)
			X = Br				
IXa	Dimethylamino	344	81	$C_{14}H_{11}N_5O_2S_2Br_2$	33.4	2.4	13.7
					(33.3	2.2	13.9)
IXb	Diethylamino	340	83	$C_{16}H_{15}N_5O_2S_2Br_2$	36.3	2.8	13.4
					(36.0	2.8	13.1)
IXc	Dibenzylamino	320	84	$C_{26}H_{19}N_5O_2S_2Br_2$	47.6	3.0	10.4
					(47.5	2.9	10.7)
IXd	Diethanolamino	335	82	$C_{16}H_{15}N_5O_4S_2Br_2$	33.8	2.5	12.1
					(34.0	2.7	12.4)
IXe	Piperidino	316	79	$C_{17}H_{15}N_5O_3S_2Br_2$	36.2	2.9	12.7
					(36.4	2.7	12.5)
IXf	Morpholino	242	74	$C_{16}H_{13}N_5O_3S_2Br_2$	35.3	2.6	12.5
					(35.1	2.4	12.8)
IXg	N-Methylpiperazino	291	83	$C_{17}H_{16}N_6O_2S_2Br_2$	36.6	2.6	15.3
					(36.4	2.9	15.0)
IXh	N-Phenylpiperazino	290	86	$C_{22}H_{18}N_6O_2S_2Br_2$	42.7	2.7	13.3
					(42.4	2.9	13.5)
IXi	N-(*p*-Chlorophenyl)-piperazino	314	85	$C_{22}H_{17}N_6O_2S_2Br_2Cl$	40.3	2.4	12.6
					(40.2	2.6	12.8)
IXj	N-Methylanilino	319	79	$C_{19}H_{13}N_5O_2S_2Br_2$	40.4	2.4	12.6
					(40.2	2.3	12.3)
IXk	N-Ethylanilino	305	77	$C_{20}H_{15}N_5O_2S_2Br_2$	41.1	2.3	12.3
					(41.3	2.6	12.0)

*Melting points were determined in open capillary tubes in a conc. H_2SO_4 bath and are uncorrected.

position-3 of rhodanine nucleus are more active than those carrying arylamino substituents at this position.

Antiviral activity—The method of Varma and Awasthi[7] was employed for determining the antiviral activity. Compounds VIIIi, IXf, IXi and IXj showed better antiviral potentiality against Gompherna Mosaic Virus, while others were moderately active. The antiviral screening results presented in Table 2 indicate that the compounds with dibromo substituted quinazolone ring (X = Br) are more potent than the unsubstituted analogs and the 'piperazino' and 'arylamino' Mannich bases are more active than the dialkylamino Mannich bases.

Table 2—Antibacterial and Antiviral Activities of 3-(N,N-Disubstituted aminomethyl)-5-[(6,8-disubstituted-4-oxoquinazolin-3-yl)imino]-4-oxo-1,3-thiazolidine-2-thiones (VIII and IX)

Compd	$N<^{R^1}_{R^2}$	Inhibition zone (cm) against bacteria					Inhibition (%) of Gompherna Mosaic Virus (at 2.5 mg/ml conc.)
		B. cereus	*S. aureus*	*M. flavus*	*S. lutea*	*B. subtilis*	
				X = H			
VIIIa	Dimethylamino	1.1	1.1	0.9	0.6	—	ns
VIIIb	Diethylamino	0.8	0.8	1.0	—	—	11
VIIIc	Dibenzylamino	.....	.....	ns	.....	.....	12
VIIId	Diethanolamino	0.7	—	0.8	—	—	ns
VIIIe	Piperidino	.....	.....	ns	.....	.....	ns
VIIIf	Morpholino	.....	.....	ns	.....	.....	ns
VIIIg	N-Methylpiperazino	0.8	1.1	—	0.6	—	ns
VIIIh	N-Phenylpiperazino	0.8	0.9	1.3	—	—	ns
VIIIj	N-(*p*-Chlorophenyl)-piperazino	.....	.....	ns	.....	.....	39
VIIIj	N-methylanilino	0.7	—	—	0.6	—	26
VIIIk	N-ethylanilino	0.7	0.8	0.6	—	—	ns
				X = Br			
IXa	Dimethylamino	—	0.7	0.6	—	—	ns
IXb	Diethylamino	—	0.8	0.6	—	—	24
IXc	Dibenzylamino	—	0.8	—	0.6	—	ns
IXd	Diethanolamino	—	0.7	—	0.7	—	ns
IXe	Piperidino	—	0.8	—	0.6	—	29
IXf	Morpholino	—	—	—	1.0	—	40
IXg	N-Methylpiperazino	—	0.7	—	—	—	ns
IXh	N-Phenylpiperazino	0.6	0.9	—	—	—	ns
IXi	N-(*p*-Chlorophenyl)-piperazino	—	0.9	—	1.0	—	46
IXj	N-Methylanilino	—	0.8	—	0.7	—	65
IXk	N-Ethylanilino	.....	.....	ns	.....	.....	ns
Tetracycline (Standard)		3.6	2.4	2.5	2.4	2.0	

ns = not screened; (−) = no activity

The required 6,8-disubstituted quinazolin-4(3*H*)-ones[8] (I,II) and 4-oxothiazolidine-2-thione[3] (V) were prepared by known methods.

3-Nitrosoquinazolin-4(3H)-ones (III and IV)

To a solution of quinazolin-4(3*H*)-one (0.05 mol) in acetic acid (40 ml) was added sodium nitrite (0.1 mol) in small portions (0.5 g each) with vigorous shaking in ice. The solution thus obtained was kept at room temperature overnight and then poured into crushed ice. The solid separated was filtered, washed well with water and recrystallised from ethyl acetate to get III (X = H), yield 82%, m.p. 263° (Found: C, 54.6; H, 2.7; N, 24.2. $C_8H_5N_3O_2$ requires C, 54.9; H, 2.9; N, 24.0%); IR: 3050 (aromatic C−H), 1690 (quinazolinone C=O) and 1515 cm^{-1} (N=O).

Similarly, 3-nitroso-6,8-dibromoquinazolin-4(3*H*)-one (IV; X = Br) was prepared by the nitrosation of 6,8-dibromoquinazolin-4(3*H*)-one, and recrystallised from ethyl acetate, yield 81%, m.p. 280° (Found: C, 23.5; H, 0.8; N, 13.4. $C_6H_3N_3O_2Br_2$ requires C, 23.3; H, 1.0; N, 13.6%).

5-(4-Oxoquinazolin-3-yl)imino-4-oxothiazolidine-2-thiones (VI and VII)

3-nitrosoquinazolin-4(3*H*)-one (III, 0.05 mol) was dissolved in acetic acid (10 ml) containing acetic anhydride (1 ml). To this solution, 4-oxothiazolidine-2-thione (V; 0.05 mol) and sodium acetate (5 g) were added and the reaction mixture was refluxed on a sand-bath for 6 hr and subsequently poured into ice cold water. The solid thus separated was filtered, washed well with water, dried and recrystallised from ethyl acetate to get VI, yield 70%, m.p. 286° (Found: C, 45.4; H, 2.2; N, 19.4. $C_{11}H_6N_4O_2S_2$ requires C, 45.5; H, 2.1; N, 19.3%); IR(KBr): 3400 (N−H), 3050 (aromatic C−H), 1690 (C=O), 1610 (C=N) and 1230 cm^{-1} (C=S) etc.

Similarly, 5-(6,8-dibromo-4-oxoquinazolin-3-yl)-4-oxothiazolidine-2-thione (VII) was prepared from IV and V, yield 74%, m.p. >300 (Found: C, 29.3; H, 0.7; N, 12.3. $C_{11}H_4N_4O_2Br_2S_2$ requires C, 29.5; H, 0.9; N, 12.5%).

5-[(4-*Oxoquinazolin*-3-*yl*)*imino*]-4-*oxo*-3-(*N-phenylpiperazinomethyl*)-1,3-*thiazolidine*-2-*thione* (*VIIIh*)

To a suspension of VI (0.005 mol) in methanol (10 ml) was added formalin (37%; 0.008 ml) while warming followed by the addition of N-phenylpiperazine (0.005 mol) with stirring and heating. The crystallization was induced by scratching. The solution was allowed to stand at room temperature overnight. The solid thus separated was filtered, washed with pet. ether, dried in air, and recrystallised from DMF, yield 80%, m.p. 286° (Found: C, 56.7; H, 4.5; N, 18.3. $C_{22}H_{20}N_6O_2S_2$ requires C, 56.9; H, 4.3; N, 18.1%); IR(KBr): 3050 (aromatic C−H), 2900 (aliphatic C−H), 1700 (C=O), 1620 (C=N) and 1240 cm^{-1} (C=S) etc; PMR(DMSO) δ 2.25 [*t*, 4H, $C_6H_5N(CH_2)_2$], 2.75 [*t*, 4H, $CH_2N(CH_2)_2$], 3.80 (*s*, 2H, N−CH_2−N) and 6.9-8.2 (complex *m*, 10H, Ar−H).

In a similar manner other members of VIII and IX were prepared. Their characterisation data are given in Table 1.

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Synthesis of Some 2-Amino- & 2-Mercapto-4-chromanylthiazoles & Their Derivatives as Antifungal & Antibacterial Agents

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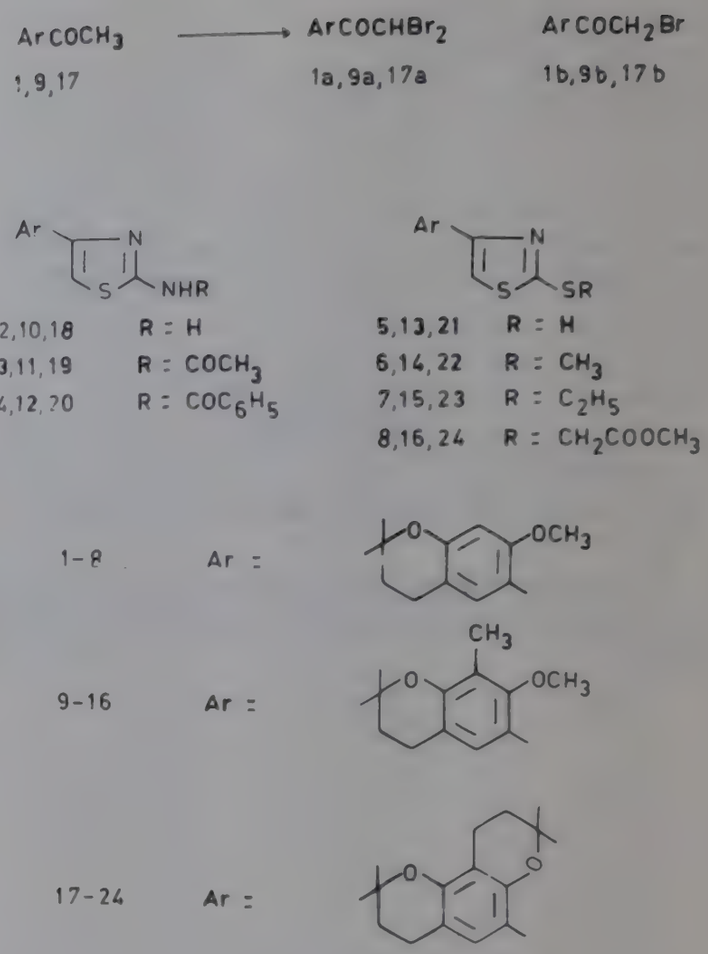
Bromination of 6-acetylchromans (**1**, **9**, **17**) gives a mixture of monobromo (major) and dibromo (minor) acetyl derivatives. The monobromoacetyl derivatives (**1b**, **9b**, **17b**) on condensation with thiourea afford 2-amino-4-chromanylthiazoles (**2**, **10**, **18**). These 2-aminothiazoles are also obtained when the corresponding 6-acetylchromans (**1**, **9**, **17**) are condensed with thiourea in the presence of iodine. Acetylation and benzoylation of 2-aminothiazoles afford the corresponding acetyl (**3**, **11**, **19**) and benzoyl (**4**, **12**, **20**) derivatives. Condensation of monobromoacetylchromans (**1b**, **9b**, **17b**) with ammonium dithiocarbamate affords the corresponding 2-mercaptothiazoles (**5**, **13**, **21**). 8-Methyl, 8-ethyl and S-carbomethoxymethyl derivatives of 2-mercaptothiazoles have also been prepared. All the thiazoles synthesised (**2-8**, **10-16**, **18-24**) have been tested for their antifungal and antibacterial activities.



The biological importance of chromans[1] as well as thiazoles[2] prompted us to construct molecules possessing both the ring systems. With this aim in view, some 2-amino- and 2-mercapto-thiazoles bearing 2,2-dimethylchromans at 4-position have been synthesised.

Condensation of 6-acetyl-7-methoxy-2,2-dimethylchroman (**1**)[3] with thiourea in the presence of iodine using benzene as solvent gave a product whose IR spectrum showed absorptions at 3410 and 3290 cm^{-1} (NH_2 stretching) and PMR spectrum exhibited a broad singlet for two protons at δ 5.02 (exchangeable with D_2O) due to NH_2 function and one-proton singlet at δ 6.87 due to thiazole H-5 besides other signals for the chroman moiety. The spectral data as well as the elemental analysis were suggestive of the structure 2-amino-4-(7′-methoxy-2′,2′-dimethylchroman-6′-yl)thiazole (**2**).

Bromination of **1** with bromine in carbon tetrachloride gave a 1:9 mixture of two compounds which were separated by column chromatography over silica gel. Both the compounds gave positive DNP reaction. In the IR spectrum of the first (minor) compound, the carbonyl absorption band was observed at 1680 cm^{-1} and in the PMR spectrum a one-proton singlet was observed at δ 7.02 assignable to $COCHBr_2$ proton, besides other usual signals. Hence it was assigned the structure 6-dibromoacetyl-7-methoxy-2,2-dimethylchroman (**1a**). The IR spectrum of the second (major) compound displayed the carbonyl absorption band at 1675 cm^{-1}. In its PMR spectrum a two-proton singlet appeared at δ 4.53 due to $COCH_2Br$ protons besides the usual signals. On this basis it was assigned the structure 6-bromoacetyl-7-methoxy-2,2-dimethylchroman (**1b**).

6-Bromoacetylchroman (**1b**) on condensation with thiourea in abs. ethanol afforded 2-amino-4-(7′-methoxy-2′,2′-dimethylchroman-6′-yl)thiazole (**2**), identical (m.p., m.m.p. and co-IR) with the sample obtained above.

Acetylation of **2** with acetic anhydride gave 2-acetylamino-4-(7′-methoxy-2′,2′-dimethylchroman-6′-yl-) thiazole (**3**) and benzoylation of 2 with benzoyl chloride in pyridine gave 2-benzoylamino-4-(7-methoxy-2′,2′-dimethylchroman-6′-yl)thiazole (**4**). The structures assigned to **3** and **4** were in agreement with their elemental analysis and spectral data.

6-Bromoacetylchroman (**1b**) on condensation with ammonium dithiocarbamate in abs. ethanol afforded a pale yellow product which was assigned the structure 2-mercapto-4-(7′-methoxy-2′,2′-dimethoxychroman-6′-yl)thiazole (**5**) on the basis of its elemental analyses, IR spectrum (2490 cm^{-1} due to −SH stretching) and

the PMR spectrum exhibiting, besides other signals, a one-proton singlet at δ 6.64 due to thiazole H-5. Reaction of **5** with dimethyl sulphate, ethyl iodide and methyl chloroacetate afforded the corresponding S-methyl (**6**), S-ethyl (**7**) and S-carbomethoxymethyl (**8**) derivatives. Structures assigned to all these compounds (**6-8**) were in agreement with their elemental analyses and spectral data. Similarly 2-amino- (**10** and **18**) and 2-mercapto- (**13** and **21**) thiazoles have been synthesised starting from 6-acetyl-7-methoxy-2,2,8-trimethylchroman (**9**)[4] and 3,4,9,10-tetra-hydro-2,2,8,8-tetramethyl-2H,8H-benzo[1,2-*b*; 3,4-*b'*]-dipyran (**17**)[3] through bromo derivatives (**9b** and **17b**). The amino thiazoles obtained were converted into N-acetyl (**11** and **19**) and N-benzoyl (**12** and **20**) derivatives. The mercaptothiazoles were converted into S-methyl (**14** and **22**), S-ethyl (**15** and **23**) and S-carbomethoxymethyl (**16** and **24**) derivatives. Melting points and yields of all the compounds are given in Table 1.

Table 1—Melting Points and Yields of the Various Compounds Prepared

Compd*	Yield† (%)	m.p.‡ (°C)	Compd*	Yield† (%)	m.p.‡ (°C)
1a	6	111-12	**13**	76	162-63
1b	72	103-4	**14**	86	74-75
2	88	162-64	**15**	91	70-71
3	87	198-99	**16**	83	84-85
4	74	166-67	**17a**	7	120-21
5	71	197-98	**17b**	73	128-29
6	86	78-79	**18**	77	98-100
7	91	oil	**19**	91	135-36
8	80	95-97	**20**	73	205-7
9a	6	109-10	**21**	83	219-19
9b	71	oil	**22**	95	101-2
10	95	184-85	**23**	86	84-85
11	87	211-13	**24**	83	87-88
12	70	194-97			

*Satisfactory microanalyses were obtained for all the compounds.
†Yields for compounds **1a**, **1b**, **9a**, **9b**, **17a**, and **17b** are based on the corresponding acetylchromans whereas for **2**, **5**; **10**, **13**; and **18**, **21** are with respect to **1b**, **9b** and **17b** respectively.
‡Melting points are uncorrected.

Biological activity

All the thiazole derivatives synthesised were tested for their antifungal activity[5] against *Aspergillus niger* and *Aspergillus fumigatus* and for antibacterial activity[6] against *Staphylococcus aureus* and *Escherichia coli* at 25μg/ml and 50μg/ml concentrations. The results indicate that almost all the compounds show marginal antibacterial activity and comparatively better antifungal activity. Compounds **2**, **4**, **7** and **18** showed 65% or above inhibition at 50 μg/ml against *Aspergillus fumigatus* as compared to bavistin, taken as standard, which under the experimental conditions showed above 96% inhibition against both the fungal species.

Procedures for one typical case is described. IR spectra were recorded on a Perkin-Elmer 621 spectrophotometer and PMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer.

Condensation of 6-*acetyl*-7-*methoxy*-2,2-*dimethylchroman* (**1**) *with thiourea*: *Formation of* 2-*amino*-4-(7'-*methoxy*-2',2'-*dimethylchroman*-6'-*yl*)*thiazole* (**2**)

Compound **1** (1 g) in dry benzene (25 ml) was refluxed with thiourea (0.65 g) and iodine (1.08 g) for 36 hr and the solvent distilled off. The residue obtained was washed repeatedly with ether and extracted with hot water. Treatment of the aq. extract with liquor ammonia yielded a solid which was filtered, washed with water, dried and crystallised from ethanol to give **2** as light yellow prisms.

Bromination of 6-*acetyl*-7-*methoxy*-2,2-*dimethylchroman* (**1**) *with bromine in carbon tetrachloride*

Bromine (1.37 g as 10% solution in carbon tetrachloride) was added dropwise to a solution of **1** (2 g) in carbon tetrachloride with stirring at 30-35° during 40 min and solvent distilled off. The residue thus obtained was found to be a mixture of two products. It was subjected to column chromatography and the column eluted successively with (i) benzene-pet. ether (1 : 19) and (ii) benzene: pet. ether (1 : 9) giving the following two fractions.

Fraction I—Crystallised from benzene-pet. ether yielding **1a** as colourless shining crystals.

Fraction II—It crystallised from benzene-pet. ether yielding **1b** as colourless shining needles.

Condensation of 6-*bromoacetyl*-7-*methoxy*-2,2-*dimethylchroman* (**1b**) *with thiourea*: *Formation of* **2**

The bromoacetylchroman **1b** (1 g) in abs. ethanol (25 ml) was refluxed with thiourea (0.26 g) for 4 hr and the solvent distilled off. The solid, obtained after the addition of crushed ice and liquor ammonia was filtered, washed with water, dried and crystallised from ethanol to give **2** as light yellow prisms.

Condensation of **1b** *with ammonium dithiocarbamate*: *Formation of* 2-*mercapto*-4-(7'-*methoxy*-2',2'-*dimethylchroman*-6'-*yl*)*thiazole* (**5**)

Ammonium dithiocarbamate (0.39 g) was added to a solution of **1b** (1 g) in abs. ethanol (50 ml) with stirring and the mixture refluxed for 1 hr and solvent distilled off. The residue was refluxed with benzene (10 ml) and the salt filtered off. The filtrate on cooling gave **5** as pale yellow prisms.

The financial assistance provided by ICAR, New Delhi is gratefully acknowledged.

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Substituted Cinnamide 4-Sulfonyl Derivatives

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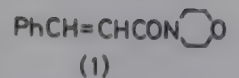
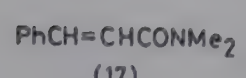
Cinnamoylmorpholine (**1**) and the dimethylamide (**17**) react with chlorosulfonic acid to give the 4-sulfonyl chlorides (**2**, **18**). Twenty seven sulfonyl derivatives have been derived from **2** and **18** by reacting these with nucleophilic reagents. The results of preliminary antibacterial and fungicidal screening of the sulfonyl derivatives are included.

Cinnamic acid, cinnamide and chalcone are known[1-4] to react with chlorosulfonic acid to yield the *p*-sulfonyl chlorides. Several cinnamide sulfonyl derivatives prepared in our laboratory were found[3] to possess antibacterial and fungicidal activities. As an extension of this work, in this note we present our results on the chlorosulfonation of cinnamoylmorpholine[5] (**1**) and the dimethylamide (**17**) and the biological activities of the various sulfonyl derivatives prepared. Chlorosulfonation of **1** was best carried out using 6 molar equivalent of chlorosulfonic acid and keeping the reaction mixture at room temperature for one week when **2** was obtained in 60% yield. The dimethylamide (**17**), on the other hand, on heating with 6 molar equivalent of the reagent at 70° (3 hr) gave a good yield (72%) of N,N-dimethylcinnamide-4-sulfonyl chloride (**18**). Cinnamoylmorpholine-4-sulfonyl chloride (**2**) was reacted with amines (2 mol), hydrazine hydrate (3 mol) and sodium azide (2 mol), under standard conditions, to give the derivatives (**3-8**, **15**). The hydrazide (**8**) was characterized as the hydrazones (**9-14**) and the azide (**15**) was reacted with norbornene to give the aziridine (**16**) (Table 1). Similarly **18** was condensed with amines, hydrazine, sodium azide and N,N-dimethylhydrazine to give compounds (**19-24**, **30-31**). The hydrazide (**24**) was reacted with carbonyl compounds to give the hydrazones (**25-29**) (Table 1). However, **24** on reaction with acetylacetone in boiling ethanol (5 hr) afforded a mixture of two products (2 spots on TLC); these are probably the hydrazone and the 3,5-dimethylpyrazole derivative. The IR spectrum indicated the presence of NH and CO groups while the PMR spectrum displayed four different methyl proton signals. On the other hand, the mass spectrum only showed the molecular ion corresponding to the 3,5-dimethylpyrazole derivative (M^+, 333).



(1)



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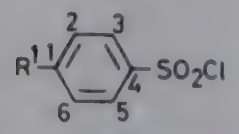
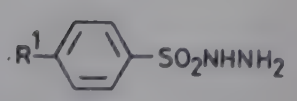
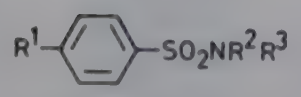


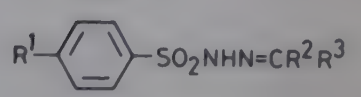
(2)(18)



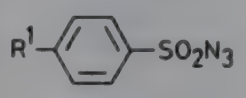
(8)(24)



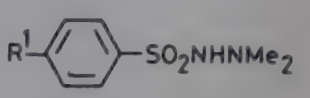
(3)(19) $R^2=R^3=Me$
(4)(23) $R^2=R^3=$morpholino
(5) $R^2=H, R^3=Ph$
(6) $R^2=R^3=$piperidino
(7)(21) $R^2=H, R^3=CH_2Ph$
(20) $R^2=R^3=H$
(22) $R^2=R^3=Et$



(9)(25) $R^2=R^3=Me$
(10)(26) $R^2=H, R^3=Ph$
(11)(27) $R^2=H, R^3=C_6H_4NO_2$-p
(12)(28) $R^2=H, R^3=C_6H_4OMe$-p
(13) $R^2=H, R^3=C_6H_4Cl$-p
(14)(29) $R^2, R^3=-(CH_2)_4-$



(15)(30)



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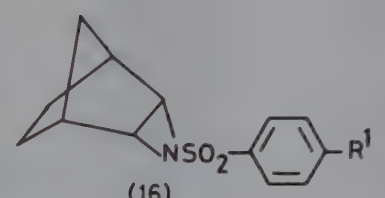


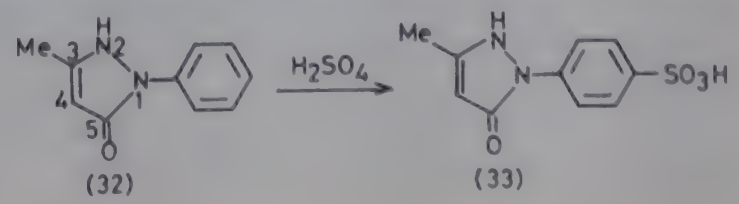
(16)

(2-16) $R^1=CH=CHCON$ O
(18-31) $R^1=CH=CHNMe_2$

It is likely that the hydrazone would cyclise in the mass spectrometer. Attempted reactions of the morpholinoazide (**30**) with triethyl phosphite or norbornene (1 mol) gave uncrystallisable oils (cf. ref. 3).

3-Methyl-1-phenyl-5-pyrazolone[6] (**32**) was sulfonated as described by Ioffe and Khavin[7] to give the corresponding 4-sulfonic acid (**33**). The PMR spectrum of **33** displayed aromatic resonances (δ 8.1-7.5) as a well-defined AA^1BB^1 pattern confirming *p*-sulfonation. Subsequent attempts to convert **33** into the sulfonyl chloride by treatment with chlorosulfonic acid failed, probably due to zwitterion formation between the NH and SO_3H groups. This problem has been previously observed[8] in the reaction of some arylureas with chlorosulfonic acid.

The assigned structures are supported by microanalytical, IR, PMR and MS data. The electron impact mass spectra of the majority of compounds showed the molecular ion peaks (M^+). However, these were not observed with the hydrazides and hydrazones



(32) (33)

Table 1—Substituted Cinnamide-*p*-sulfonyl Derivatives

Compd	Yield (%)	m.p. (°C)	Mol. formula	Found (%)			Reqd (%)		
				C	H	N	C	H	N
3[a]	55	149-150	$C_{15}H_{20}N_2O_4S$	55.4	6.4	8.8	55.6	6.2	8.6
4	45	242-244	$C_{17}H_{22}N_2O_5S$	55.5	5.7	7.3	55.7	6.0	7.7
5	32	199-200	$C_{19}H_{20}N_2O_4S$	61.0	5.4	7.2	61.3	5.4	7.5
6	36	166-167	$C_{18}H_{24}N_2O_4S$	59.1	6.7	7.5	59.3	6.6	7.7
7	82	142	$C_{20}H_{22}N_2O_4S$	62.1	5.8	6.0	62.2	5.7	5.8
8	72	150-152	$C_{13}H_{17}N_3O_4S$	49.9	5.7	13.3	50.2	5.5	13.5
9	88	192	$C_{16}H_{21}N_3O_4S$	54.5	6.1	12.2	54.7	6.0	12.0
10	63	200-201	$C_{20}H_{21}N_3O_4S$	59.8	5.3	10.7	60.2	5.3	10.5
11	80	229-231	$C_{20}H_{20}N_4O_6S$	53.8	4.6	12.5	54.0	4.5	12.6
12	78	200-201	$C_{21}H_{23}N_3O_5S$	58.3	5.4	9.9	58.7	5.4	9.8
13	77	220-221	$C_{20}H_{20}ClN_3O_4S$	55.7	4.6	9.7	55.4	4.6	9.7
14	90	198-200	$C_{18}H_{23}N_3O_4S$	57.0	6.2	11.0	57.3	6.1	11.1
15	51	82-84	$C_{13}H_{14}N_4O_4S$	48.2	4.7	17.2	48.4	4.3	17.4
16	83	151-153	$C_{20}H_{24}N_2O_4S$	62.1	6.2	7.4	61.9	6.2	7.2
19	97	165-166	$C_{13}H_{18}N_2O_3S$	55.4	6.4	9.8	55.3	6.4	9.9
20	72	218-219	$C_{11}H_{14}N_2O_3S$	52.4	5.7	10.8	52.0	5.6	11.0
21	80	194-195	$C_{18}H_{20}N_2O_3S$	62.6	5.8	8.4	62.8	5.8	8.1
22	73	95-96	$C_{15}H_{22}N_2O_3S$	57.7	7.0	8.7	58.1	7.1	9.0
23	62	181	$C_{15}H_{20}N_2O_4S$	55.8	6.3	8.6	55.6	6.2	8.6
24	71	155-156	$C_{11}H_{15}N_3O_3S$	48.9	5.3	15.9	49.1	5.6	15.6
25	84	202-203	$C_{14}H_{19}N_3O_3S$	54.0	6.0	13.4	54.4	6.2	13.6
26	56	231	$C_{18}H_{19}N_3O_3S$	60.3	5.2	11.9	60.5	5.3	11.8
27	90	228-229	$C_{18}H_{18}N_4O_5S$	53.5	4.3	13.7	53.7	4.5	13.9
28	92	203	$C_{19}H_{21}N_3O_4S$	58.6	5.2	10.9	58.9	5.4	10.9
29	58	202	$C_{16}H_{21}N_3O_3S$	57.3	6.3	12.5	57.4	6.3	12.5
30	69	116-118	$C_{11}H_{12}N_4O_3S$	46.6	4.0	19.7	47.1	4.3	20.0
31	49	118-182	$C_{13}H_{19}N_3O_3S$	52.8	6.6	13.8	52.5	6.4	14.1

(a) PMR(DMSO-d_6): δ 8.2-7.7 (*m*, 4ArH), 7.52-7.49 (*d*, CH=CH), 3.70-2.85 (*m*, 8H, morpholino H), 2.6 (*s*, NMe_2).
MS: *m/z* 324 (M^+), 238 ($M-C_4H_8NO$), 216 ($M-SO_2NMe_2$), 108 (Me_2NSO_2), 86($C_4H_8NO_7$), 76(C_6H_4).

which suffered extensive fragmentation, in agreement with previous observations[9].

Biological activity

The compounds were screened for antibacterial activity by innoculation of agar plates following the procedure of Steers *et al.*[10] and the results were compared with penicillin as standard (100% control). The test organisms used were *Streptococcus faecalis*, *Clostridium perfringens* and *Staphylococcus aureus*. At 50 ppm complete inhibition of the bacteria was shown by the compounds: **8**, **15**, **24**, **25** and **30**.

The *in vitro* antifungal screening was performed using the standard glass slide spore germination test as described by Kirby and Frick[11]. At 100 ppm against *Botrytis cinerea*, high activity was observed for compounds, **8**, **24**, **9**, **25** and **13**. Compounds were also examined at 1000 ppm against *Aspergillus versicolor*, *Cladosporium cladosporiodes*, *Penicillium purpurogenum*, *Phoma violacea*, *Stachybotrys chartatum* and *Ulocladium atrum*; compounds **9**, **25** and **27** were active against all 6 test fungi.

Melting points were determined with a Gallenkemp electric apparatus and are uncorrected.

Chlorosulfonation of cinnamoylmorpholine (**1**)

Cinnamoylmorpholine (**1**, 15 g) was reacted with chlorosulfonic acid (48.3 g, 6 mol) at room temperature for 1 week. The solution was poured onto crushed ice (500 g) to give TLC pure **2** (13 g; 60%), m.p. 125-27°; IR: 1660 (CO), 1625 (arom C=C), 1320, 1180 (SO_2), 1120 (C-O-C) cm^{-1}; MS: *m/z* 315 (M^+), 280 (M-Cl), 229 ($M-C_4H_8NO$), 216 ($M-SO_2Cl$), 86 (C_4H_8NO).

Chlorosulfonation of N,N-dimethylcinnamide (**17**)

Dimethylcinnamide (**17**, 10 g) was heated with chlorosulfonic acid (41.4 g, 6 mol) at 70° for 3 hr to give TLC pure **18** as a cream powder (11.2 g; 72%), m.p. 145-47°; IR: 1660 (CO), 1615 (arom C=C), 1350, 1170 (SO_2), 1110 (C-O-C) cm^{-1}; MS: *m/z* 273 (M^+), 229 ($M-NMe_2$), 174 ($M-SO_2Cl$), 131 (PhCH=CHCO), 103 (PhCH=CH).

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Some Reactions of 4-Chlorosulfonyl-α-naphthylchalcone

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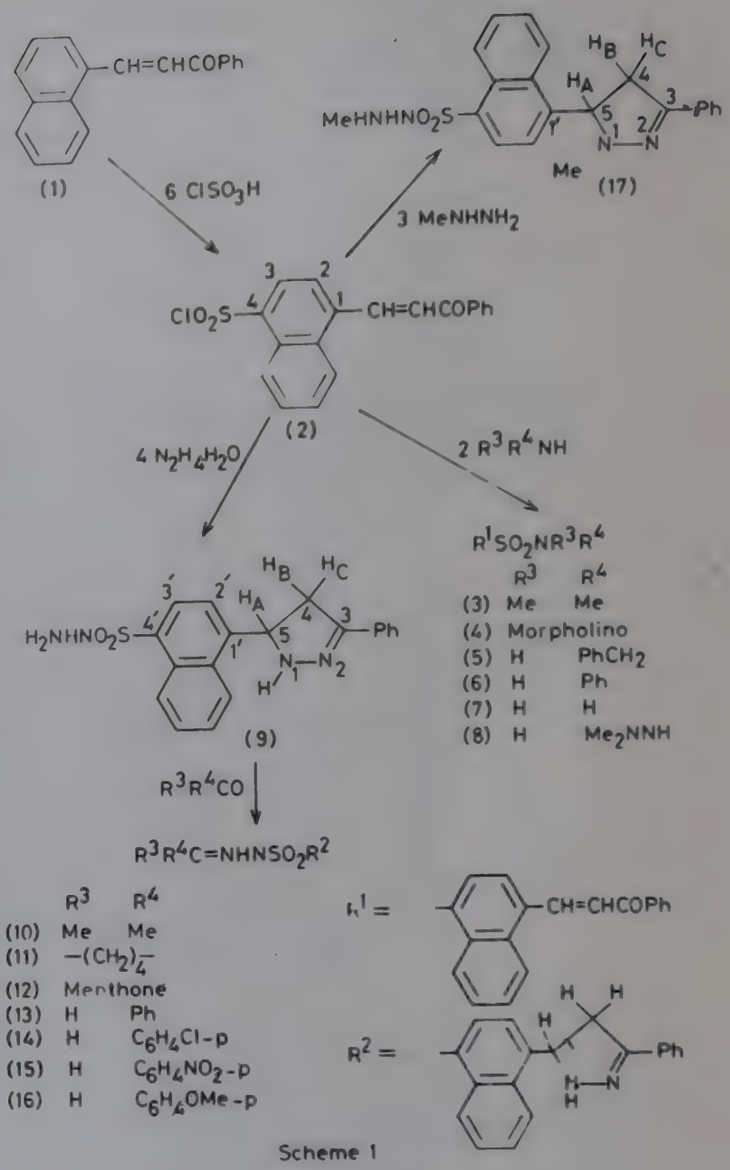
4-Chlorosulfonyl-α-naphthylchalcone (**2**) has been prepared and characterised as the sulfonamides (**3-7**). With N,N-dimethylhydrazine, **2** gives the chalconedimethylhydrazide (**8**); reaction with hydrazine and N-methylhydrazine affords the pyrazolines (**9**,**17**) and the hydrazones (**10-16**). Reaction of α-naphthylchalcone (**1**) with hydrazine results in the pyrazoline (**18**). The results of preliminary antibacterial and fungicidal screening are included.

This note forms part of our general programme on the chemistry and biocidal activity of aromatic sulfonyl derivatives[1-6], including chalcone and 4-methoxychalcone sulfonyl derivatives[5]. Chalcones are potential biocides, because some naturally-occurring antibiotics[6] and aminochalcones[7,8] probably owe their biological activity to the presence of the α,β-unsaturated carbonyl group. Misra[9,10] prepared naphthylchalcones by base-catalysed condensation of benzaldehydes with substituted naphthyl methyl ketones; in this work α-naphthylchalcone (**1**) was obtained from α-naphthaldehyde and acetophenone.

The optimum conditions for the chlorosulfonation of α-naphthylchalcone (**1**) involved its treatment with 6 molar equivalents of chlorosulfonic acid at room temperature for 1 day, in contrast to three weeks required for the chlorosulfonation of some chalcones as reported earlier from our laboratories. This may be attributed to the greater reactivity of the naphthalene nucleus towards electrophilic attack. By analogy with the chlorosulfonation of chalcone[5], it would be expected that chlorosulfonation of **1** would occur in the 4-position of the naphthalene ring and this orientation is supported by consideration of the Hammett substituent constants[11].

Thus **1** reacted with excess chlorosulfonic acid under mild conditions to give 4-chlorosulfonyl-α-naphthylchalcone (**2**) in 76% yield. **2** was condensed with dimethylamine, morpholine, benzylamine, aniline and ammonia to give the amide (**3-7**) (Scheme 1). Reaction of **2** with N,N-dimethylhydrazine afforded the dimethylhydrazide (**8**); on the other hand, reaction with hydrazine resulted in cyclisation to form the pyrazoline sulfonylhydrazide (**9**), which was condensed with aldehydes and ketones to give the hydrazones (**10-16**). Reaction with N-methylhydrazine similarly afforded the N-methylpyrazoline (**17**). These



Scheme 1

results are similar to those previously reported[5] for *p*-chlorosulfonylchalcone. In the case of N,N-dimethylhydrazine, cyclisation to the pyrazoline ring does not occur because of the absence of a free NH group. The structures of all the compounds were fully supported by their PMR and mass spectral data. The mass spectra of the compounds (Table 1) generally showed the molecular ions (M^+), with the exception of the hydrazides and hydrazones which suffered extensive fragmentation as has been previously observed[12].

Our attempts to synthesise naphthalene pyrazoline sulfonyl derivatives by an alternative approach involving reaction of α-naphthylchalcone (**1**) with hydrazine to give α-naphthylpyrazoline (**18**) followed by treatment with chlorosulfonic acid to yield the sulfonyl chloride (**19**) were unsuccessful. This procedure, if successful might have provided a wide range of sulfonyl derivatives, many of which such as

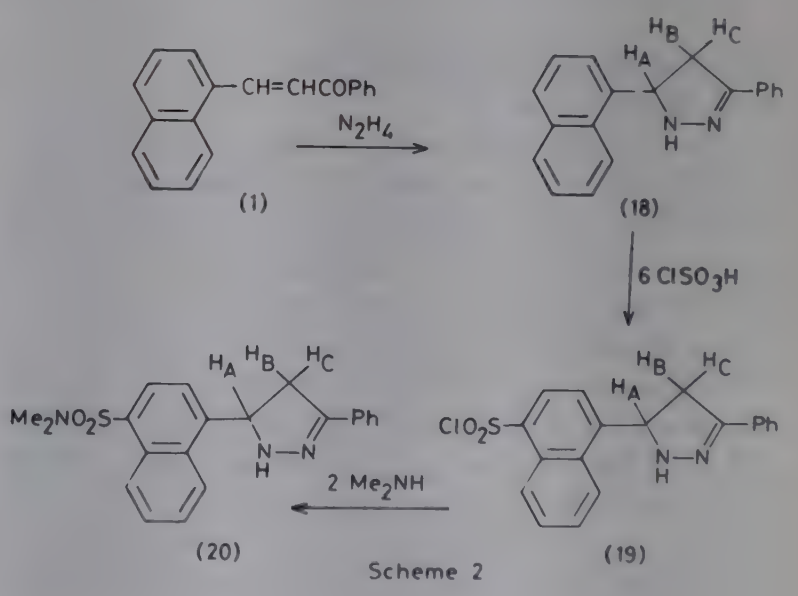
Table 1—α-Naphthylchalcone Sulfonyl Derivatives

Compd	m.p. °C	Yield %	Mol formula (M⁺)	Found (%) / (Calc.)		
				C	H	N
3	68-70	46	$C_{21}H_{19}NO_3S$ (365)	68.8 (69.0)	5.3 (5.2)	4.1 (3.8)
4	112-14	54	$C_{23}H_{21}NO_4S$ (407)	67.5 (67.8)	5.5 (5.2)	3.4 (3.4)
5	141-42	78	$C_{26}H_{21}NO_3S$ (427)	72.8 (73.0)	4.6 (4.9)	3.3 (3.2)
6	123-25	83	$C_{23}H_{19}NO_3S$ (413)	71.6 (71.8)	4.8 (4.7)	3.6 (3.5)
7	170-72	34	$C_{19}H_{15}NO_3S$ (337)	67.9 (67.7)	4.7 (4.6)	4.3 (4.2)
10	153-54	52	$C_{22}H_{22}N_4O_2S$	65 (65.0)	5.6 (5.4)	13.5 (13.8)
11	224-26	39	$C_{24}H_{24}N_4O_2S$	66.3 (66.6)	5.2 (5.6)	13.4 (13.0)
12	158-61	27	$C_{28}H_{32}N_4O_2S$	68.6 (68.9)	6.4 (6.6)	11.2 (11.5)
13	169-71	62	$C_{26}H_{22}N_4O_2S$	68.4 (68.7)	4.9 (4.8)	12.3 (12.3)
14	171-73	96	$C_{26}H_{21}ClN_4O_2S$	62.5 (62.7)	4.3 (4.4)	11.0 (11.2)
15	167-69	84	$C_{26}H_{21}N_5O_4S$ $\frac{1}{2}H_2O$	61.1 (61.4)	4.4 (4.5)	13.9 (13.8)
16	164-65	69	$C_{27}H_{24}N_4O_3S$ $\frac{1}{2}H_2O$	65.4 (65.7)	4.9 (5.1)	11.4 (11.35)
17	182-84	39	$C_{21}H_{22}N_4O_2S$ $\frac{1}{2}H_2O$	63.7 (64.0)	5.5 (5.6)	14.4 (14.2)

the dimethylamide (**20**) would not be obtainable by the first route. The problems associated with the alternative approach probably arise from the relative instability of the pyrazoline (**18**) (rapidly turns yellow; TLC 2 spots) which probably suffers rupture of the NH-N bond in the presence of the strongly acidic chlorosulfonic acid (Scheme 2).

Biological activity

The compounds were screened for antibacterial activity by innoculation of agar plates following the procedure of Steers *et al.*[13] and the results compared with penicillin as standard (100% control). In the preliminary antibacterial tests against *Streptococcus faecalis*, *Clastridium perfringens* and *Staphylococcus aureus* at 100 ppm, the most active compounds against the bacteria were **3**, **7** and **9**. The *in vitro* fungicidal screening was carried out using the standard glass slide spore germination method as described by Kirby and Frick[14]. In the antifungal tests against *Botrytis cinerea* at 100 ppm, the most potent compounds were **8**, **9**, **10** and **17**. The compounds were also examined against the fungi *Aspergillus vericolor*, *Cladosporium cladosporioides*, *Penicillium purpurogenum*, *Phoma violacea*, *Stachybotrys chartatum* and *Ulocladium atrum* at 1000 ppm, but only compound **2** was active.



Scheme 2

α-Naphthylchalcone (**1**)

α-Naphthaldehyde (33.5g, 0.21 mol) and acetophenone (25.8g, 0.21 mol) were stirred with a mixture of ethanol (100 ml) and 10% aq sodium hydroxide (150 ml) in an ice-salt bath for 4 hr. The crystals were filtered off, washed with water, pet ether (40-60°)-ether (1:1) (20 ml) and air-dried to give **1** as yellow needles (48g, 87%), m.p. 81-82° (lit.[15] m.p. 82-82.5°); IR: 1660 (CO), 1605 cm^{-1} (arom C=C); PMR ($CDCl_3$): δ 8.8-8.6 (*d*, 2H, CH=CH, J_{HH}=15 Hz), 8.3-7.2 (*m*, 12H,

ArH); ^{13}C NMR ($CDCl_3$): δ 190.5 (*s*, CO), 134-123.5 (*m*, arom C); MS: *m/z* 258 (M^+), 257 (M-H), 229 (M, $-H$ $-CO$), 181 ($C_{12}H_9CO$), 105 (PhCO).

4-Chlorosulfonyl α-naphthylchalcone (**2**)

α-Naphthylchalcone (10.1g, 0.04 mol) was gradually added to chlorosulfonic acid (15 ml, 0.24 mol) with swirling and cooling (ice-bath) such that the temperature was kept < 10° during addition. After 24 hr at room temperature, the dark brown solution was added to ice (400g) to give TLC pure **2** (10.6g, 76%), m.p. 118-20°; IR: 1665 (CO), 1609 (arom C=C), 1345, 1150 cm^{-1} (SO_2); MS: *m/z* 358, 356 (M^+), 227 (M $-SO_2Cl$ $-CO$), 152 ($C_{12}H_8$). 105 (PhCO).

General procedure for reaction of **2** *with amines*

The sulfonyl chloride (**2**) (0.005 mol) was reacted with the amine (0.01 mol) in methanol (10 ml). The solution was cooled (0°) during the initial reaction and was left at room temperature (3 hr). The mixture was poured onto crushed ice (20g) and the precipitated sulfonamides (**3-7**) were purified by recrystallization from aq methanol. PMR, IR and mass spectral data of a typical compound (**3**) are as follows: PMR ($CDCl_3$): δ 8.93-7.3 (*m*, 13H, ArH, CH=CH), 2.83 (s, 6H, NMe_2); IR: 1665 (CO), 1610 (arom C=C), 1340, 1155 cm^{-1} (SO_2); MS: *m/z* 365 (M^+), 257 ($M-SO_2NMe_2$), 152 ($C_{12}H_8$), 105 (PhCO).

4-(N,N-Dimethylhydrazinosulfonyl)-α-naphthylchalcone (**8**)

To a stirred ice-cold solution of **2** (1.5g, 0.0042 mol) in THF (20 ml), was added N,N-dimethylhydrazine (0.77g, 0.013 mol). After standing at 10° overnight, the solid product was filtered off, washed with water (2 × 10 ml) and dried to give **8** as orange plates (1g, 62%), m.p. 148-150°. It was found to give a single spot on TLC (Found: C, 66.0; H, 5.1; N, 7.6. $C_{21}H_{20}N_2O_3S$ requires C, 66.3; H, 5.3; N, 7.4%); IR: 3220 (NH), 1650 (CO), 1609 (arom C=C), 1345, 1147 cm^{-1} (SO_2); PMR (DMSO-d_6): δ 8.9-7.2 (*m*, ArH, CH=CH), 5.5(*s*, 1H, NH), 2.3 (*s*, 6H, NMe_2); MS: no M^+ (380), other peaks at *m/z* 284, 257 ($M-SO_2$ $NH-NMe_2$), 105(PhCO).

3-Phenyl-5-(4'-hydrazinosulfonyl α-naphthyl)pyrazoline (**9**)

To a stirred ice-cold solution of **2** (5g, 0.014 mol) in methanol (20 ml) was added hydrazine hydrate (2.8g of 98%, 0.056 mol). After 3 hr at room temperature, the mixture was poured onto ice (30g), the product was filtered off and washed with water (2 × 10 ml) to give **9** as a fawn powder (2.01g, 39%), m.p. 167-70 (decomp.). It was found to give one spot on TLC (Found: C, 62.0; H, 4.8; N, 15.1. $C_{19}H_{18}N_4O_2S$ requires C, 62.3; H, 4.9 N, 15.3%IR: 3380, 3330 (NH_2), 3260 (NH), 1596 (arom C=C), 1350, 1140 cm^{-1} (SO_2); PMR (DMSO-d_6); δ 10.5(*s*, 1H, SO_2NH), 8.8-7.3 (*m*, 12H, ArH, NH), 5.6 (*t*, 1H, H_A), 3.8-2.7 (*d*, 2H, H_B H_C); MS: no M^+ (366), other peaks at *m/z* 302 ($M-SO_2$), 276, 152, 115, 91.

The sulfonyl hydrazide (**9**) was condensed with aldehydes and ketone (1 mol equiv.) in methanol at room temperature (3 hr) to give the hydrazones (**10-16**) (Table 1). Typical spectra of **10** are as follows: PMR(DMSO-d_6): δ 10.45(*s*,1H,SO_2NH), 8.78-7.12 (*m*,12H,ArH,NH), 5.51(*t*,1H,H_A),3.86-2.6(*d*,2H,H_BH_C), 1.9(*d*,6H, NMe_2); IR: 3400(NH), 1610(arom C=C), 1575 (C=N), 1350, 1135 cm^{-1}(SO_2); MS: no M^+(406), other peaks at *m/z* 271 ($M-SO_2NHN=CMe_2$), 91.

3-Phenyl-5-(4-N-methylhydrazinosulfonyl-α-naphthyl)pyrazoline (**17**)

The sulfonyl chloride (**2**, 5g, 0.014 mol) was reacted with N-methylhydrazine (1.95g, 0.042 mol) in methanol (15 ml) at room temperature for 3 hr. The mixture was poured onto ice (30g) and washed with water (2 × 15 ml) to give the TLC pure **17**; IR: 3400-3300 (NH), 1590 (arom C=C), 1350, 1150 cm^{-1} (SO_2); PMR (DMSO-d_6): δ 10.8 (*s*, 1H, SO_2NH), 9.0-7.1 (*m*, 11H, ArH); 6.22 (*s*, 1H, MeN*H*), 5.9-5.7 (*t*, 1H, H_A), 4.13-3.5 (*d*, 2H, H_B, H_C), 2.76 (*s*, 3H, Me).

α-Naphthylchalcone pyrazoline (**18**)

α-Naphthylchalcone (**1**, 3.2g, 0.012 mol) was stirred with hydrazine hydrate (2.5g of 98%, 0.048 mol) at room temperature for 4 hr. At the end of the reaction, the initial yellow colour had disappeared and the solution was poured onto ice (50g). The precipitate was filtered off, washed with water (10 ml) and methanol (2 × 10 ml) to give **18** as colourless needles which gradually turned yellow (2.26g, 70%), m.p. 101-3°. TLC showed 2 spots (Found: C, 83.2; H, 5.5; N, 10.0. $C_{19}H_{16}N_2$ requires C, 83.8; H, 5.9; N, 10.3%); IR: 3320 (NH), 1595 (arom C=C), 1572 cm^{-1} (C=N), PMR (DMSO-d_6): δ 8.15-7.54 (*m*, 13H, ArH, NH) 5.96-5.7 (*t*, 1H, H_A), 3.9-2.92 (*d*, 2H, H_B, H_C); MS: *m/z* 272 (M^+), 270 (M−2H), 145 ($C_9H_9N_2$), 105 (PhN_2).

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Synthesis & Biological Activity of 2-Aryloxyalkyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles

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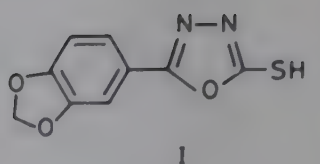
4-Amino-5-mercapto-3-(3,4-methylenedioxyphenyl)-1,2,4-triazole (II) reacts with various aryloxyalkyl carboxylic acids to yield 2-aryloxyalkyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (III). Interesting profiles of analgesic and anti-inflammatory activities have been observed during primary screening of these compounds in experimental animals.

In our earlier work[1,2] we found that 2,5-disubstituted-*s*-triazolo-[3,4-*b*]-1,3,4-thiadiazoles possess strong CNS depressant, mild to moderate antiinflammatory and mild hypocholesteremic and hypotensive activities. Incorporation of appropriate aryloxyalkyl moiety in heterocyclic rings[3] such as oxadiazole and *s*-triazole has led to the compounds possessing CNS depressant, antiinflammatory and hypotensive actions. In view of antiinflammatory and antipyretic activities exhibited by compounds containing methylenedioxyphenyl group[4], we attempted to study the effect on biological activity of methylenedioxyphenyl moiety attached to a *s*-triazolothiadiazole ring. These observations prompted us to synthesise 2-aryloxyalkyl-5-(3,4-methylenedioxyphenyl) *s*-triazolo-[3,4-*b*]-1,3, 4-thiadiazoles (III) and screen them for their analgesic and antiinflammatory activities.

The synthesis of III was accomplished in one step with good yields by condensing 4-amino-5-mercapto-3-(3,4-methylenedioxyphenyl)-1,2,4-triazole (II) with various aryloxyalkyl carboxylic acids in the presence of phosphorus oxychloride (Scheme 1). The *s*-triazole II, in turn was prepared from the corresponding 1,3,4-oxadiazole (I) following the method of Heindel[5]. The characterisation data of III and their biological activity are given in Tables 1 and 2 respectively.

Primary screening results

Toxicity (LD_{50}), analgesic and antiinflammatory activities of compounds III in experimental animals were determined by literature methods[6,7]. All the compounds along with the starting material were devoid of toxicity as shown by their LD_{50} values which were more than 800 mg/kg oral (i.p. mice). It can be observed from Table 2 that compounds III_{13} and III_{15} exhibit analgesic activity (i.e. 60% and 58% respectively) similar to that of aspirin (60%) whereas the starting triazole (II) shows only 10% analgesic action. Compound III_{14} exhibits mild antiinflammatory activity (24%) in comparison to phenyl butazone (39%), while triazole II shows 15% antiinflammatory action.



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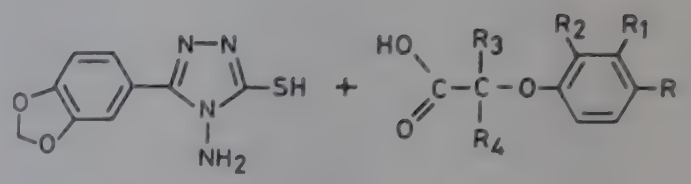
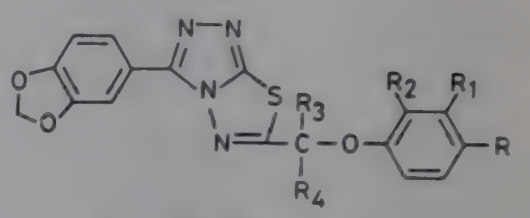


II



III (1–15 : Table 1)

R = H or Cl, R_1 = H, R & R_1 = O–CH_2–O

R_2 = H, CH_3 or Cl, R_3 & R_4 = H or CH_3

Scheme 1

It has been reported earlier[1] that 2-phenoxymethyl-5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole exhibits 11% analgesic and 10% antiinflammatory activities. However, in the present study the corresponding 2-phenoxymethyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (III_1) exhibited 21% analgesic activity and 15% antiinflammatory activity. This shows that the incorporation of a 3,4-methylenedioxy group in the phenyl ring does enhance the above activities.

The structural assignments of II and III were based on elemental analyses and IR, PMR and mass spectral data. All the compounds were checked for their purity by TLC on silica gel-G.

Melting points were taken in open capillaries on a Buchi 510 melting point apparatus and are

Table 1—Characterization Data of 2-Aryloxyalkyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (III)

Compd	R_2	R_3	R_4	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.) C	H	N
					R = R_1 = H				
III_1	H	H	H	185	75	$C_{17}H_{12}N_4O_3S$	57.0 (56.9)	3.5 3.4	15.8 15.9)
III_2	H	CH_3	H	108-10	72	$C_{18}H_{14}N_4O_3S$	59.1 (59.0)	3.9 3.9	15.3 15.3)
III_3	H	CH_3	CH_3	103-5	68	$C_{19}H_{16}N_4O_3S$	61.6 (61.6	4.4 4.4	15.2 15.1)
					R = Cl; R_1 = H				
III_4	H	H	H	198-200	73	$C_{17}H_{11}ClN_4O_3S$	52.8 (52.8	2.9 2.9	14.5 14.5)
III_5	H	CH_3	H	110	74	$C_{18}H_{13}ClN_4O_3S$	54.0 (53.9	3.3 3.3	14.0 14.1)
III_6	H	CH_3	CH_3	98-100	67	$C_{19}H_{15}ClN_4O_3S$	55.1 (55.0	3.6 3.6	13.6 13.5)
III_7	Cl	H	H	178-80	71	$C_{17}H_{10}Cl_2N_4O_3S$	48.5 (48.5	2.4 2.4	13.3 13.3)
III_8	Cl	CH_3	H	158-60	69	$C_{18}H_{12}Cl_2N_4O_3S$	49.7 (49.7	2.8 2.8	12.9 12.9)
III_9	Cl	CH_3	CH_3	134-35	66	$C_{19}H_{14}Cl_2N_4O_3S$	50.9 (50.8	3.2 3.1	12.5 12.5)
III_{10}	CH_3	H	H	108-10	72	$C_{18}H_{13}ClN_4O_3S$	54.0 (53.9	3.3 3.3	14.0 14.0)
III_{11}	CH_3	CH_3	H	118-20	71	$C_{19}H_{15}ClN_4O_3S$	55.1 (55.0	3.7 3.6	13.6 13.5)
III_{12}	CH_3	CH_3	CH_3	143-45	66	$C_{20}H_{17}ClN_4O_3S$	56.1 (56.0	4.1 4.0	13.0 13.1)
					R, R_1 = $-O-CH_2-O-$				
III_{13}	H	H	H	220-21	71	$C_{18}H_{12}N_4O_5S$	54.6 (54.5	3.1 3.0	14.1 14.1)
III_{14}	H	CH_3	H	169-70	70	$C_{19}H_{14}N_4O_5S$	55.7 (55.6	3.5 3.4	13.7 13.7)
III_{15}	H	CH_3	CH_3	179-80	65	$C_{20}H_{16}N_4O_5S$	56.6 (56.6	3.8 3.8	13.2 13.2)

Table 2—Analgesic and Antiinflammatory Activities of Compounds II and III

(Dose 100 mg/kg oral)

Compd	Analgesic action (% protection of pain)	Antiinflammatory action (% inhibition)*
II	10	15
III_1	21	15
III_2	18	17
III_3	23	15
III_5	17	18
III_{13}	60	13
III_{14}	31	24
III_{15}	58	18
Aspirin	60	—
Phenylbutazone	—	39

*The compounds which possess inhibition less than 10% have not been shown in the table.

uncorrected. IR spectra were recorded on a Perkin-Elmer 221 spectrophotometer (ν_{max} in cm^{-1}), PMR spectra on a Varian A60A spectrometer using TMS as the internal standard (chemical shift in δ, ppm) and mass spectra on a Hitachi RMU 6L mass spectrometer at 70 eV.

4-Amino-5-mercapto-3-(3,4-methylenedioxyphenyl)-1,2,4-triazole (II)

A mixture of 2-mercapto-5-(3,4-methylenedioxyphenyl)-1,3,4-oxadiazole (5 g), hydrazine hydrate (15 ml) and ethanol (60 ml) was refluxed on a steam-bath for 13 hr. The reaction mixture was concentrated, poured into ice water and acidified with acetic acid to get the product which was filtered and recrystallised from ethanol, m.p. 214-15°, yield 4 g (75%) (Found: C, 45.8; H, 3.5; N, 13.6. $C_9H_8N_4O_2S$ requires C, 45.8; H, 3.4; N, 13.5%); IR(KBr): 3300 (NH_2), 3100 (NH), 1620 (C=N) and

1550 (C=C); PMR ($CDCl_3$): 6.10 (*s*, 2H, O-CH_2-O), 7.1-7.8 (*m*, 3H, Ar-*H*), 6.9 (broad, 1H, NH) and 5.7 (broad, 2H, NH_2); MS: *m/z* 236 (M^+), 205 ($M^+ - N_2H_3$), 165 ($M^+ - CH_3N_4$), 147 ($M^+ - CH_3N_3S$), 121 ($M^+ - C_2H_3N_4S$), 221 ($M^+ - NH$), 162 ($M^+ - CH_2N_2S$), 191 ($M^+ - CHS$), 178 ($M^+ - CNS$), 177 ($M^+ - CHNS$), 161 ($M^+ - CH_3N_2S$).

4-Chloro-2-methylphenoxymethyl-5-(3,4-methylenedioxyphenyl)-s-triazolo[3,4-*b*]-1,3-4-*thiadiazole* (III_{10})

A mixture of II (4.72 g; 0.02 mol), 4-chloro-2-methylphenoxyacetic acid (4.01 g; 0.02 mol) and $POCl_3$ (20 ml) was heated under reflux for 5 hr and excess $POCl_3$ removed under reduced pressure. The concentrated mass was cooled and poured into ice cold water to give a solid product which on washing with a dil. solution of $NaHCO_3$ followed by water and recrystallisation from ethanol gave the title compound III_{10}; IR (KBr): 1630 (C=N), 1230 (ether); PMR ($CDCl_3$): 2.35 (*s*, 3H, CH_3), 5.31 (*s*, 2H, OCH_2), 5.95 (*s*, 2H, O-CH_2-O), 6.50-7.15 (*m*, 4H, 3 Ar-*H* of 2-substituent and 1 Ar-*H* of 5-substituent), 7.75-7.90 (*m*, 2H, 2 Ar-*H* adjacent to C=N); MS: *m/z* 400 (M^+), 260 ($M^+ - C_7H_5ClO$), 259 ($M^+ - C_7H_6ClO$), 155 ($M^+ - C_{10}H_5N_4O_2S$), 147 ($M^+ - C_{10}H_8ClN_3OS$), 142 ($M^+ - C_{11}H_6N_4O_2S$), 125 ($M^+ - C_{11}H_7N_4O_3S$), 121 ($M^+ - C_{11}H_8ClN_4OS$), 113 ($M^+ - C_{12}H_7N_4S_2O_2$) and 107 ($M^+ - C_{11}H_6ClN_4SO_2$).

Compounds III_1-III_9 and III_{11}-III_{15} (Table 1) were prepared in a similar manner by the reaction of II with appropriate aryloxyalkyl carboxylic acids.

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Synthesis & Antiinflammatory Activity of 1-(6′-Substituted-2′-benzothiazolyl)-3,4-dimethylpyrano[2,3-*c*]pyrazol-6(1*H*)-ones

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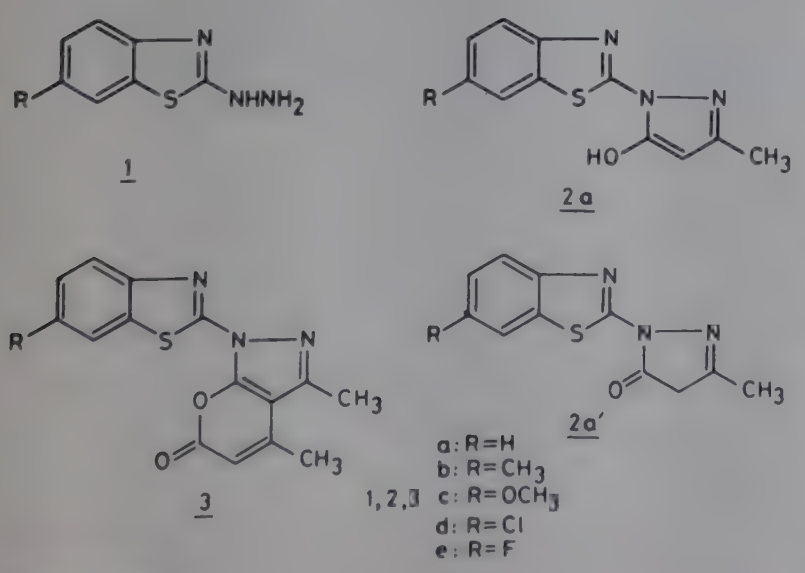
1-(6′-Substituted-2′-benzothiazolyl)-3,4-dimethylpyrano-[2,3-*c*]pyrazol-6(1*H*)-ones (**3**) have been synthesized (i) by the reaction of 2-hydrazino-6-substituted-benzothiazoles (**1**) with ethyl acetoacetate and (ii) by the reaction of 1-(6′-substituted-2-benzothiazolyl)-3-methylpyrazol-5-ols (**2**) with ethyl acetoacetate. Some of the compounds (**3a-c** and **3e**) display moderate levels of antiinflammatory activity.

Prompted by the observation that many pyrazole derivatives possess antiinflammatory activity[1-3], and in continuation of our work on benzothiazole derivatives as potential antiinflammatory agents[4-6], we have presently synthesised 1-(6′-substituted-2′-benzothiazolyl)-3,4-dimethylpyrano[2,3-*c*]-pyrazol-6(1*H*)-ones (**3a-e**) with a view to evaluating their antiinflammatory behaviour.

Condensation of 6-substituted-2-hydrazinobenzothiazoles[7,8] (**1**) with 2 mol of ethyl acetoacetate at 160° resulted in **3** in good yields (Table 1). Compounds (**3**) were also obtained by the condensation of 1-(6′-substituted-2′-benzothiazolyl)-3-methylpyrazol-5-ols[9,10] (**2**) with ethyl acetoacetate at 160°. Compounds obtained by these two approaches were identical in all respects (m.m.p. and co-IR).



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‡Lecturer in Chemistry, Department of Chemistry, H A University, Kaul (Kurukshetra).

Table 1—Physical Data of 1-(6′-Substituted-2′-benzothiazolyl)-3,4-dimethylpyrano[2,3-*c*]pyrazol-6(1*H*)-ones (**3**)

Compd (R=)	Mol. formula ($M^{+\cdot}$)	m.p. °C	Found (Calc.), %		
			C	H	N
3a (H)	$C_{15}H_{11}N_3SO_2$ (297)	274	60.58 (60.60)	3.67 (3.70)	14.11 (14.14)
3b (CH_3)	$C_{16}H_{13}N_3SO_2$ (311)	260	61.78 (61.73)	4.17 (4.18)	13.49 (13.50)
3c (OCH_3)	$C_{16}H_{13}N_3SO_3$ (327)	284	58.75 (58.71)	3.94 (3.97)	12.82 (12.84)
3d (Cl)	$C_{15}H_{10}N_3SO_2Cl$ (331)	289	54.36 (54.38)	3.01 (3.02)	12.64 (12.68)
3e (F)	$C_{15}H_{10}N_3SO_2F$ (316)	295	57.14 (57.14)	3.20 (3.17)	13.35 (13.33)

It was interesting to note that PMR spectra of **2** in neutral or basic solvent ($CDCl_3$ or DMSO-d_6) displayed signals at δ 5.25 and 14.8 integrating for one proton each assignable to 4-H and intramolecularly bonded OH, respectively, besides the other signals. However, when the spectra were taken in TFA, **2** displayed a two-proton sharp signal at δ 4.0 while the signal at δ 5.2 was absent. These observations showed that **2** existed in the enol form in $CDCl_3$ or DMSO-d_6 and in the keto form in TFA. It may be inferred that in basic or neutral solvent due to strong hydrogen bonding, the enol form exists, whereas in TFA the protonation of basic **2** prevents hydrogen bond formation, thus keto form exists. We believe that the formation of **3** from **1** occurs through the intermediacy of **2** and it is the enol form of **2** which is responsible for further reaction. Compounds of the type (**3**) thus prepared were fully characterised by their elemental analyses and IR, PMR and mass spectral data. IR spectra of **3** in nujol displayed a sharp band at 1740 cm^{-1} due to lactone carbonyl. PMR spectra of **3** in TFA displayed signals at δ 2.72, 2.78 integrating for three protons each due to two methyl groups, a singlet at 6.45 (1H, pyran 5-*H*) besides the aromatic protons and other signals. Mass spectra of **3** showed that molecular ions as the base peaks.

Four compounds, viz. **3a-c** and **3e** were subjected to preliminary screening for antiinflammatory activity by carrageenin-induced rat paw edema test following the procedure of Winter *et al.*[11], as modified by Srimal and Dhawan[12]. Compounds **3a**, **3b**, **3c** and **3e** were found to be less toxic (ALD_{50} 800, 950, 1000, 1000 mg/kg respectively). The compounds, when tested on mice for their ability to antagonise carrageenin-induced edema at 0.2 of ALD_{50} showed moderate level of

antiinflammatory activity (27, 29, 36 and 42% respectively).

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in nujol on a Beckman IR-20 spectrometer (ν_{max} in cm^{-1}), PMR spectra in $CDCl_3$ or DMSO-d_6 using TMS as internal standard on an R-32 Perkin-Elmer instrument (chemical shifts in δ, ppm), mass spectra at 70 eV on an MS-12 mass spectrometer fitted with a direct inlet system (source temperature kept at about 165°).

6-Substituted-2-hydrazinobenzothiazole[7,8] (**1**) and 1-(6′-substituted-2′-benzothiazolyl)-3-methylpyrazol-5-ols[9,10] (**2**) were prepared according to literature procedure.

1-(2′-*Benzothiazolyl*)-3,4-*dimehthylpyrano*-[2,3-*c*]*pyrazol*-6(1*H*)-*one* (**3a**)

(a) A mixture of 2-hydrazinobenzothiazole (**1**; 1.65 g, 0.01 mol) and ethyl acetoacetate (2.60 g, 0.02 mol) was heated in an oil-bath at 160° for 1 hr and the contents washed with ether. The solid thus obtained was recrystallized from DMF to afford **3a**, m.p. 274°, yield 1.72 g (58%).

(b) A mixture of 1-(2′-benzothiazolyl)-3-methyl-pyrazol-5-ol (**2a**; 2.3 g, 0.01 mol) and ethyl acetoacetate (1.3 g, 0.01 mol) was heated in an oil-bath at 160° for 1 hr, the contents washed with ether and the solid obtained recrystallized from DMF, m.p. and m.m.p. 274°; IR(nujol): 1740; (PMR(TFA): 2.72 (*s*, 3H, CH_3), 2.78 (*s*, 3H, CH_3), 6.45 (*s*, 1H, pyran-5*H*), 7.4-7.9 (*m*, 4H, aromatic protons). Other compounds **3b-e** were similarly prepared in good yields (60-70%) and were recrystallized from DMF. These compounds are listed in Table 1.

We are grateful to Prof Kurt L Loening, Nomenclature Director, Chemical Abstract Service for providing the nomenclature of title compounds, to Prof A Dondovi, University Di Ferrara—Italy for low resolution mass spectral data, to Prof B N Dhawan, CDRI, Lucknow for biological testing and to Chairman, Chemistry Department, Kurukshetra University for providing facilities.

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BOOK REVIEWS

Physical and Mechanistic Organic Chemistry by R A Y Jones (Cambridge University Press, Cambridge), 1984, pp. 426. Price £ 35.00 ($ 69.50) for hard cover and £ 14.00 ($ 27.95) for paper back.

This is a beautifully organised textbook in the field of physical and mechanistic organic chemistry. This new edition of Dr Jones' book has been carefully updated and enlarged to include many additional examples. The book is divided into two parts. The first part (139 pp) deals with the general background theories and techniques of physical organic chemistry in a well-balanced manner, through Sections 1-6, incorporating structure and mechanism, kinetic studies, linear Gibbs energy relations, acids and bases, the reaction medium and molecular orbital method respectively. In each of these sections emphasis has been laid on understanding the general principle rather than on unnecessary details. Particularly, the author has succeeded commendably in presenting a comprehensive and critical account of the development of Hammett and Taft equations along with other modifications in a reasonably simple manner in the section three. Similarly Section 6 introduces the basic framework of the perturbed molecular orbital method (PMO theory) and its applications in the quantitative theoretical understanding of various features of organic molecules as well as the symmetry control of reactions. In fact, this section serves as a useful introduction to orbital language in a modern organic chemistry course. The second part (244 pp) which runs through Sections 7-16 under the headings of aliphatic nucleophilic substitution, elimination reactions, addition to carbon-carbon double bonds, aromatic electrophilic substitution, addition to carbonyl group and related reactions, hydrolysis of carboxylic molecular rearrangements, aliphatic radical substitutions, and pericyclic reactions, relates to the applications of the methods developed in the first part to most of the important classes of organic reactions, showing clearly how their mechanisms have been established and what factors control the mechanisms in particular circumstances. All these Sections are lucidly presented and the citation of the important original literature covers even up to 1984.

The book is well printed and the formulae are exceptionally clear, and it contains a useful subject index along with the important additional references for further reading relating to each section. A book of problems with solutions is also available to accompany this textbook.

This book is highly recommended for the advanced graduates, post-graduates and research students of the Indian universities requiring clear understanding of the general principles on which the study of mechanism is based, and who will be able to apply them to most reactions of organic chemistry.

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ANNOUNCEMENT

IUPAC Recommendations on Prenol Nomenclature

The prenols are a group of alcohols containing one or more isoprene units, and are, with their esters, the biological precursors of the isoprenoids, a variety of compounds including terpenes and steroids that contain much of the carbon skeleton intact. The new recommendations do not replace any existing document, but set out to systematize existing practice, and to supplement it by paying full attention to the important stereochemistry of the prenols. The general terms are discussed and recommendations for indicating stereochemistry are made. Short-chain prenols that have established trivial names are listed, and the relationship of the prenols to the simplest juvenile hormones is indicated.

IUPAC Recommendations on the Nomenclature of Glycoproteins, Glycopeptides & Peptidoglycans

This document provides a nomenclature for carbohydrates covalently linked to proteins or peptides. Together with the glycolipids and lipopolysaccharides they comprise the more general class of compounds known as glycoconjugates. Terms are defined both for the conjugates themselves and for their carbohydrate components, and the nature of the linkage between carbohydrate and protein or peptide is discussed. The peptidoglycans, a group of glycoconjugates found only in bacterial cell walls, are included in the recommendations. A new 'Short form' is proposed for representing the structures of complex carbohydrates as compactly as possible. As no recommendations on glycoproteins, glycopeptides and peptidoglycans have been published previously by IUPAC or IUB, the new recommendations do not replace any existing document but follow established rules of biochemical nomenclature.

Comments on both the recommendations may be sent before the end of October 1986 to Dr A Cornish-Bowden, Department of Biochemistry, University of Birmingham, POB 363, Birmingham B15 2TT, UK.

Those desirous of having full texts of the above recommendations may write to the Executive Secretary, Indian national Science Academy, Bahadur Shah Zafar Marg, New Delhi 110002.

Corrigendum

Paper entitled "Synthesis, ^{13}C-NMR & Antifertility Studies of 1,2-*trans*-2-Benzyl-6-methoxy-1-(2,4-bis-substituted phenyl)indanes", *Indian J Chem*, **24B** (1985) 456-458.

The name of the author MANGEL S MALICK may be read as MANGEL S MALIK.

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